Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG2002-05

Acetamiprid
Assail Brand 70 WP Insecticide
Chipco Brand Tristar 70 WSP Insecticide
Pristine Brand RTU Insecticide

The reduced-risk insecticide acetamiprid, and the associated end-use products, Assail Brand 70 WP Insecticide for control of aphid, Colorado potato beetle and whitefly on field tomato; aphid, codling moth, leafhopper, pear psylla and tentiform leafminer on pome fruits, crop group 11; leafhopper on grapes; aphid and whitefly on cole crop group 5; aphid on leafy vegetable crop group 4; Chipco Brand Tristar 70 WSP Insecticide for control of aphid, whitefly, leafhopper, European pine sawfly and tentiform leafminer on non-food greenhouse, lathhouse, shadehouse and outdoor uses on flowering and ornamental plants; and, Pristine Brand RTU Insecticide for control of aphid, Colorado potato beetle and whitefly on field tomato; aphid, leafhopper and tentiform leafminer on pome fruit crop group 11; aphid and whitefly on cole crop group 5; aphid on leafy vegetable crop group 4; and aphid, European pine sawfly, leafhopper, whitefly and tentiform leafminer on outdoor flowering and ornamental plants have been granted temporary registration under Section 17 of the Pest Control Products Regulations.

This regulatory note provides a summary of data reviewed and the rationale for the regulatory decision for these products.

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Publications Coordinator
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6605C
Ottawa, Ontario
K1A 0K9

Internet: pmra_publications@hc-sc.gc.ca
www.hc-sc.gc.ca/pmra-arla/
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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued temporary registrations for the reduced-risk insecticide acetamiprid, manufactured by Aventis Canada Inc. and the associated end-use products, Assail Brand 70 WP Insecticide for control of aphid, Colorado potato beetle and whitefly on field tomato; aphid, codling moth, leafhopper, pear psylla and tentiform leafminer on pome fruit (crop group 11); leafhopper on grapes; aphid and whitefly on cole crops (crop group 5); aphid on leafy vegetables (crop group 4); Chipco Brand Tristar 70 WSP Insecticide for control of aphid, whitefly, leafhopper, European pine sawfly and tentiform leafminer on non-food greenhouse, lathhouse, shadehouse and outdoor uses on flowering and ornamental plants; and Pristine Brand RTU Insecticide for control of aphid, Colorado potato beetle and whitefly on field tomato; aphid, leafhopper and tentiform leafminer on pome fruit (crop group 11); aphid and whitefly on cole crops (crop group 5); aphid on leafy vegetables (crop group 4) and aphid, European pine sawfly, leafhopper, whitefly and tentiform leafminer on outdoor flowering and ornamental plants.

The company provided adequate data to support the registration of the leafy vegetable crop group 4: amaranth leafy, arugula, cardoon, celery, celery (Chinese), celtuce, chervil, chrysanthemum (edible-leaved), chrysanthemum (garland), corn salad, cress (garden), cress (upland), dandelion leaves, dock, endive, fennel (Florence), lettuce (head and leaf), orach, parsley leaves, purslane (garden), purslane (winter), radicchio, rhubarb, spinach, spinach (New Zealand), spinach (vine), Swiss chard; the cole crop group 5: broccoli, broccoli (Chinese), broccoli raab, Brussels sprouts, cabbage, cabbage (Chinese, bok choy), cabbage (Chinese, napa), cabbage (Chinese mustard, gai choy), cauliflower, cavalo broccolo, collards, citrus (dried pulp), kale, kohlrabi, mizuna, mustard greens, mustard spinach, rape greens, and the pome fruit crop group 11: apple, crabapple, pear, pear (oriental) and quince for both Assail Brand 70 WP Insecticide and Pristine Brand RTU Insecticide.

These products were reviewed jointly by Health Canada's Pest Management Regulatory Agency and the United States Environmental Protection Agency (U.S. EPA), as reduced-risk products (Group 1B Joint Reviews (Reduced Risk Chemicals), which contain products with more than one active ingredient and two end-use products or more) within the North American Free Trade Agreement's Technical Working Group on Pesticides Joint Review Program.

Methods for analyzing acetamiprid in environmental media are available to research and monitoring agencies upon request to the PMRA.

Aventis Canada Inc. will be carrying out additional studies as a condition of this temporary registration. Following the review of this information, the PMRA will publish a proposed registration decision document and request comments from interested parties before proceeding with a final regulatory decision.

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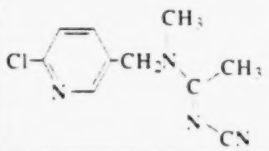
1.0 The active substance, its properties, uses, proposed classification and labelling

1.1 Identity of the active substance and preparation containing it

Table 1.1 Identity of the active substance and preparation containing it

Active substance	**Acetamiprid**
Function	Insecticide
Chemical name 1. International Union of Pure and Applied Chemistry	(*E*)-N^1-[(6-chloro-3-pyridyl)methyl]-N^2-cyano-N^1-methyl acetamidine
2. Chemical Abstract Services (CAS)	(*E*)-*N*-[(6-chloro-3-pyridinyl)methyl]-N^1-cyano-N^1-methyl ethanimidamide
CAS number	135410-20-7
Molecular formula	$C_{10}H_{11}ClN_4$
Molecular weight	222.68
Structural formula	
Purity of active	99.5% nominal (upper certified limit (UCL) = 100.0%, lower certified limit (LCL) 99.0%)
Identity of relevant impurities of toxicological, environmental and (or) other significance	Based on the starting material and the manufacturing process used, Toxic Substances Management Policy (TSMP) Track-1 substances as identified in Appendix II of Dir99-03, *Toxic Substances Management Policy*, are not expected to be present in the product.

1.2 Physical and chemical properties of active substance

Table 1.2 Technical product: Acetamiprid

Property	Result	Comment
Colour and physical state	Very pale yellow powder	
Odour	No characteristic odour	
Melting point or range	98.9°C	
Boiling point or range	N/A	
Specific gravity	1.330 at 20°C	
Vapour pressure	$<1 \times 10^{-6}$ Pa (1×10^{-8} mm Hg)	Relatively nonvolatile
Henry's Law Constant at 20°C	4.189×10^{-3} Pa	Nonvolatile from water and moist soil
Ultraviolet (UV) – visible spectrum	pH / Molar absorptivity (ϵ) Neutral: 1.94×10^4 (247 nm); 1.21×10^4 (217 nm) Acidic: 1.96×10^4 (248 nm); 1.21×10^4 (215 nm) Basic: 1.91×10^4 (246 nm)	Not likely to phototransform in the environment
Water solubility (mg/L) at 25°C	pH / Solubility distilled H_2O: 4.25×10^3 5.0: 3.48×10^3 7.0: 2.95×10^3 9.0: 3.96×10^{-3} Buffer solutions are used at pH 5, 7 and 9	Very soluble
Solubility in organic solvents at 25°C	Solvent / g/100 mL Benzene: 2.44 Xylene: 4.01 *N*-hexane: 6.54 ppm CS_2: 507 ppm Acetone, methanol, ethanol, dichloromethane, chloroform, acetonitrile, tetrahydrofuran, each at >20 g/100 mL	

Property	Result	Comment
n-Octanol–water partition coefficient at room temperature	K_{ow} = 6.27	No potential for bioaccumulation
Dissociation constant	pK_a = 0.7 at 25°C	Potential for mobility in soil
Stability (temperature, metal)	Stable under all environmental conditions	

Table 1.3 End-use product Assail Brand 70 WP insecticide

Property	Result
Colour[a]	Off-white (BF) Light grey (AF)
Odour	No odour
Physical state	Solid, fluffy
Formulation type	Wettable powder
Guarantee	70.0% nominal (UCL = 73.0%, LCL = 67.0%)
Formulants	The product does not contain any EPA List 1 formulants or formulants known to be TSMP Track-1 substances.
Container material	Water soluble packs or polyethylene lined foil packed
Bulk density	22.0 lb/cu. ft (BF) 15.7 lb/cu. ft (AF)
pH (1% aqueous solution)	8.64 (BF) 7.19 (AF)
Oxidizing or reducing action	None
Storage stability	Product is stable when stored for 4 weeks at 54°C. ***A one-year storage stability study was not submitted.***
Explodability	Dust explosion constant K_{st} = 96 bar m/s This K_{st} value indicates capability for a weak explosion.

[a] BF, basic formulation; AF, alternate formulation

Table 1.4 End-use products: Pristine Brand RTU Insecticide

Property	Result
Colour	Water clear
Odour	No odour
Physical state	Liquid
Formulation type	Liquid
Guarantee	0.006% nominal (UCL = 0.008%, LCL = 0.005%)
Formulants	The product does not contain any EPA List 1 formulants or formulants known to be TSMP Track-1 substances.
Container material	Plastic
Specific density	1
pH (1% aqueous solution)	4.5
Oxidizing or reducing action	None
Storage stability	Product is stable when stored for 4 weeks at 54°C. ***A 1-year storage stability study was not submitted.***
Explodability	N/A

1.3 Details of proposed uses and further information

Assail Brand 70 WP Insecticide (Commercial class) is a wettable powder formulation of acetamiprid. This product is for control of insect pests on agricultural food crops. The proposed use-site category (USC) for this product is USC 14, terrestrial food crops.

Chipco Brand Tristar 70 WSP Insecticide (Commercial class) is a wettable powder formulation of acetamiprid packaged in water soluble packaging. The formulation is identical to that of Assail Brand 70 WP. Chipco Brand Tristar 70 WSP is for control of insect pests on greenhouse and outdoor non-food flowering and ornamental plants. The proposed USCs for this product are USC 6, greenhouse non-food crops, and USC 27, ornamentals outdoor.

Pristine Brand RTU Insecticide (Domestic class) is a ready-to-use (RTU) product (no dilution is required) of acetamiprid for control of insect pests on terrestrial food crops as

well as on non-food outdoor ornamentals. The proposed USCs for this product are USC 14, terrestrial food crops, and USC 27, ornamentals outdoor.

See Section 7.1.1 for detailed information on the proposed uses and application rates as well as seasonal maximum rates of the two products.

2.0 Methods of analysis

2.1 Methods for analysis of the active substance as manufactured

See Appendix I for summary tables.

2.2 Method for formulation analysis

See Appendix I for summary tables.

2.3 Methods for residue analysis

2.3.1 Multi-residue methods for residue analysis

The petitioner submitted data concerning the recovery of residues of acetamiprid using *Food and Drugs Act* (FDA) multiresidue method protocols (PAM Vol. I).

Protocol A
The test substance is not an *N*-methylcarbamate structure and is not naturally fluorescent; therefore, the balance of Protocol A was not required.

Protocol C
Gas chromatographic screenings were conducted with acetamiprid dissolved in acetone. Electron capture and nitrogen phosphorous detection were used for the test substance under Protocol C. The results from gas chromatographic investigations are reported as a ratio of peak retention time in minutes relative to that of the marker chemical, chlorpyrifos. Since the test substance was chromatographic, testing under Protocols D, E and F was conducted.

Protocol D
Recovery testing through the complete method without the Florisil cleanup for nonfatty matrices was conducted using a DB-1 column with nitrogen phosphorus detection. Oranges were selected as the non-fatty food sample. Duplicate orange samples were fortified with acetamiprid at 0.05 and 0.25 ppm. Recoveries ranged from 0.0 to 41.2% in four samples; average recovery of acetamiprid was 21.6 ± 20.7%.

Protocol E
Acetamiprid was analyzed for recoveries from the Florisil column using the methodology of Protocol E 303/Protocol F 304 C1 and C2. Duplicate Florisil columns were loaded

with the test substance and eluted per the respective methods. For C1, recoveries ranged from 0.0 to 20.4%. For C2, recoveries ranged from 0.0 to 11.3%. Because recoveries through both elution systems were <30%, further work was discontinued.

Protocol F
Recovery of acetamiprid was <30% using Protocol E; thus an evaluation through Protocol F was not conducted.

Existing multiresidue methods of analysis that are currently in common usage were not found to be suitable for the determination of acetamiprid residues.

2.3.2 Methods for residue analysis of plants and plant products

The petitioner is proposing two methods for the analysis of acetamiprid in plants: vegetable and non-citrus fruit matrices, and citrus fruit matrices. These plant methods analyse for parent only and, as they do not contain a hydrolysis step, they are unlikely to determine conjugated residues.

Vegetable and non-citrus fruits (Method 1)
Samples of non-citrus fruits and vegetables are extracted with methanol and filtered. Dry matrices (<20% moisture) required hydration prior to extraction. The filtered extract is diluted with aqueous sodium chloride (brine) and partitioned with hexane (discarded fraction). The brine:methanol phase is collected and partitioned twice with dichloromethane (DCM). The DCM phase is decanted through anhydrous sodium sulfate, mixed with Florisil, and evaporated to dryness. The dried Florisil, containing the adsorbed analyte, is then added to a column of fully activated Florisil. Acetamiprid residues are eluted from the column with hexane and acetone:hexane (50:50, v:v), the eluate evaporated to dryness, and residues dissolved in ethyl acetate:hexane (50:50, v:v). Further purification is achieved using a silica gel column (10% deactivated silica gel 60) using ethyl acetate as the eluant. The eluate is evaporated to dryness, redissolved in acetone, and analyzed for acetamiprid residues by gas chromatography (GC) using a DB-1701 column and an electron capture detector (ECD).

Representative chromatograms of a variety of control crop matrices (celery, cotton gin trash, pear, pepper, raisin, raisin pomace and tomato paste) showed no interferences from crop components or from reagents, solvents and glassware; peak shape was good. Adequate linearity (correlation coefficient = 0.9990) was observed in the range of 0.01–0.10 μg/mL (ppm) for acetamiprid using Method 1. The petitioner also demonstrated adequate recovery from acetamiprid fortifications up to 10 ppm.

The method limit of quantitation (LOQ) for acetamiprid was reported as 0.01 ppm for fruits (non-citrus) and vegetable commodities. The standard deviations measured with respect to recoveries following spiking at the LOQ were indicative of the method having adequate repeatability.

Citrus fruits (Method 2)

Samples of citrus fruits are extracted with acetonitrile (ACN) and filtered. Dry matrices (<20% moisture) required hydration prior to extraction. The filtered extract is diluted with aqueous sodium chloride (brine) and partitioned with hexane (discarded fraction). The brine:ACN phase is collected and partitioned three times with DCM. The DCM phase is decanted through anhydrous sodium sulfate, and evaporated to dryness. The dried DCM phase is dissolved in acetone:hexane (4:16, v:v) and subjected to Florisil column cleanup. Residues are eluted from the Florisil column with acetone:hexane (50:50, v:v). The eluate is evaporated to dryness and residues are redissolved in ACN and further purified on a tC-18 solid phase extraction column with water:ACN (85:15, v:v) as the eluant. The eluate is diluted with water:ACN (85:15, v:v) for quantitation by high performance liquid chromatography (HPLC). Residues are quantitated by HPLC using a Zorbax ®, SB-Phenyl column, a UV detector (254 nm), and an isocratic or gradient mobile phase of water, ACN and tetrahydrofuran.

Representative chromatograms of a variety of control crop matrices (grapefruit, lemon, orange, orange juice, orange dry pulp and orange oil) showed no interferences from crop components or from reagents, solvents and glassware; peak shape was good. Adequate linearity (correlation coefficient = 0.9982) was observed in the range of 0.05–0.20 μg/mL (ppm) for acetamiprid using Method 2. The petitioner also demonstrated adequate recovery from acetamiprid fortifications up to 10 ppm. The method LOQ for acetamiprid was reported as 0.05 mg/kg for citrus fruits. The standard deviations measured with respect to recoveries following spiking at the LOQ were indicative of the method having adequate repeatability.

2.3.3 Methods for residue analysis of food of animal origin

The petitioner is proposing two methods for the analysis of acetamiprid in livestock matrices (ruminant and poultry). These methods provides data separately for Acetamiprid as well the metabolite IM-2-1. As none of the methods contain a hydrolysis step, they are unlikely to determine conjugated residues.

Both methods are very similar; matrices are combined with Celite and ACN. Residues of acetamiprid and its metabolite IM-2-1 are extracted by maceration, filtered and concentrated by rotary evaporation. For fat, samples are combined with ACN and warmed in a water bath until the fat has melted and then the residues of acetamiprid and its metabolite IM-2-1 are extracted by maceration, refrigerated until the fat solidified, filtered, and concentrated by rotary evaporation. Concentrated residues are diluted with aqueous sodium chloride and partitioned twice with hexane (hexane phase discarded) and three times with DCM. The DCM phases are decanted through anhydrous sodium sulfate and evaporated to dryness. The dried organic phase is dissolved in hexane:acetone (80:20, v:v) and subjected to Florisil column cleanup. Residues are eluted from the Florisil column with hexane:acetone (1:1, v:v). The Florisil column eluate is evaporated to dryness, redissolved in water using an ultrasonic bath, and further purified using an octadecyl cartridge (C18) with water:ACN (85:15, v:v) as the eluant. The final extract is

quantitated by HPLC using a Zorbax® SB-Phenyl column, a UV detector (254 nm), and a mobile phase of water:ACN:tetrahydrofuran (75:20:5; v:v:v).

In the method used in the analysis of poultry samples, the retention time is approximately 11.25 min for acetamiprid and 8.95 min for IM-2-1. Representative chromatograms of control eggs, muscle, fat and liver showed no background interferences; peak shapes in fortified samples were good. An external standard was used. Adequate linearity (correlation coefficient > 0.999 for each analyte) was observed in the range of 0.01–0.5 ppm and 0.05–2 ppm for acetamiprid and its metabolite IM-2-1, respectively. The method LOQs for acetamiprid and its metabolite IM-2-1 were each established at 0.01 ppm for eggs, muscle and fat, and at 0.05 ppm for liver. The standard deviations measured with respect to recoveries following spiking at the LOQ did appear to be indicative of the method having adequate repeatability.

In contrast to the method used in the analysis of poultry samples, the method used for the analysis of ruminant fractions had retention times of approximately 10.75 min for acetamiprid and 8.5 min for IM-2-1. The chromatograms showed no interference in the area of the analytes, with good peak shape. Representative chromatograms of control eggs, muscle, fat and liver showed no background interferences; peak shapes in fortified samples were good. An external standard was used. Adequate linearity (correlation coefficient > 0.99[illegible]r each analyte) was observed in the range of 0.01–0.5 ppm and 0.05–2 ppm for acetamiprid and its metabolite IM-2-1, respectively. The method LOQs for acetamiprid and its metabolite IM-2-1 were each established at 0.01 ppm for milk, muscle and fat, and at 0.05 ppm for liver and kidney. The standard deviations measured with respect to recoveries following spiking at the LOQ did appear to be indicative of the method having adequate repeatability.

3.0 Impact on human and animal health

3.1 Effects having relevance to human and animal health arising from exposure to the active substance or to impurities in the active substance or to their transformation products

3.1.1 Absorption, distribution, metabolism and excretion

Metabolism studies were conducted on NI-25 (acetamiprid technical, all >99% a.i. in the form of pyridine ring-labelled [^{14}C]-NI-25 of radiochemical purity 97.1–99.8%; cyano-labelled [CN-^{14}C]-NI-25 of radiochemical purity 98.5–99.2% and unlabelled NI-25) in male and female Sprague-Dawley rats as follows:

1. **Single-dose metabolism study** (MRID 44988505)

   (1) Group A. 1 mg/kg [^{14}C]-NI-25 i.v. to 5 males and 8 females (excretion kinetics, quantitative analysis of metabolites)

(2) Group B. 1 mg/kg [^{14}C]-NI-25, by gavage to 5 rats/sex (excretion kinetics, metabolite analysis), 5 rats/sex (blood levels) and 9 rats/sex (tissue distribution)

(3) Group D. 50 mg/kg [^{14}C]-NI-25 by gavage to 5 rats/sex (blood levels), 5 rats/sex (excretion rate, metabolite analysis) and 9 rats/sex (tissue distribution)

(4) Group CN-B. 1 mg/kg [CN-^{14}C]-NI-25 by gavage to 5 rats/sex (blood levels) and 5 rats/sex (excretion rate and metabolite analysis)

2. **15-day repeated dose study** (MRID 44988506)

Absorption, metabolism, tissue distribution and metabolites were evaluated in the following groups:

(5, 6, 7) Groups I, II, III. 1 mg/kg [^{14}C]-NI-25 by gavage for 15 days to 3 rats/sex and terminated at 1, 10 and 96 h after dose 15, respectively

(8, 9) Groups IV, V. 1 mg/kg NI-25 (unlabelled) by gavage for 14 days, followed by 1 mg/kg [^{14}C]-NI-25 on day 15 to 5 rats/sex and terminated at 96 and 48 h, respectively (excretion kinetics, tissue distribution, metabolite analysis)

(10) Group VI. 0.9% saline to 2 rats/sex, controls, sacrificed at 96 h

3. **Biliary excretion study** (MRID 44988507)

(11) Group BII. 1 mg/kg [^{14}C]-NI-25 by gavage to 4 bile-duct cannulated rats/sex for collection of bile at 3, 6, 12, 24 and 48 h postdosing, plus collection of urine, feces, liver and GI tract

(12) Group BI. 2/sex saline controls

4. **Metabolite characterization** (MRID 44988504)

(13) Group C. Quantitative and qualitative identification of urinary and fecal metabolites using samples from Group IV. MRID 44988503 provided an overview of these studies.

There were no treatment related toxicologic effects. Recovery of administered radioactivity for all groups was between 89.6 and 106% (except Group V, which was 71.6–85.6%, due possibly to the loss of the urine sample). Absorption of orally administered NI-25 was rapid and complete. Estimation of absorption by comparison of urinary excretion following intravenous (i.v.) and oral administration (i.e., [urinary excretion oral/urinary excretion, i.v.] × 100) indicated 96–99% absorption following oral administration. This was consistent with urinary excretion, cage wash and tissue/body burden data from the repeated dose experiments, showing ~65–75% absorption. There did not appear to be biologically relevant gender related differences. Pharmacokinetic parameters reflected the rapid absorption and excretion. Peak blood concentrations

occurred within 1–2 h for the low-dose (1 mg/kg) groups and only slightly later (~4 h) for the high-dose (50 mg/kg) group. Clearance from the blood was nearly complete by 48 h. Tissue half-lives ranged from 3.5 to 5.9 h for males and 2.9 to 7.9 h for females in the low-dose group, and from 6.0 to 8.5 h for males and 6.3 to 8.3 h for females in the high-dose group, suggesting that tissue elimination was not greatly affected by a 50-fold dose increment. Consistent with rapid and complete excretion, the time-course in tissues was similar to that for blood. There was no evidence for sequestration of radioactivity and no significant gender related differences. Pharmacokinetic parameters derived from the 15-day repeat-dose study were similar to the single-dose study.

Urinary excretion was the major route of elimination of [^{14}C]- NI-25. Excretion of NI-25 was rapid regardless of dose or label position, with most (76–97%) of the urinary excretion occurring within 24 h in the single oral dose groups. Urinary excretion following i.v. dosing was similar to the oral route. Repeat dosing also resulted in rapid and complete urinary excretion (most within 24 h). Fecal excretion accounted for approximately 12–17% of a single oral or i.v. dose of the ring-labelled test article but only about 5% of the cyano-labelled material. After repeat dosing, fecal excretion accounted for between 21 and 35% of the administered radioactivity, with males being slightly higher (most groups 33–35% vs. 22–29%, females). Fecal excretion of radioactivity by rats in the biliary elimination study was expectedly less; 6.72% (males) and 5.84% (females). Biliary elimination exhibited considerable individual variability, although mean biliary excretion of radioactivity did not vary notably between genders. By 48 h, biliary elimination accounted for approximately 19% of the administered radioactivity.

Tissue distribution data for the repeat-dose study showed a wide distribution but tissue burdens were low (generally <1% of the administered dose). The greatest radioactivity was expectedly found in the gastrointestinal tract (including lumen contents), where up to 3–4% of the administered dose was detected in Group I. Liver and kidney also exhibited somewhat greater levels of radioactivity than did other tissues but did not exceed 0.66% of the dose and declined notably from 1 to 96 h following the last of 15 doses. At 96 h postdosing (Groups II and IV), radioactivity levels in most tissues were <0.007% of the administered dose. There was no significant difference between whole blood radioactivity and plasma radioactivity. No gender related differences were observed. Tissue levels of radioactivity in the single-dose and biliary excretion studies showed a similar pattern. The data indicate that 15-day repeat doses of 1 mg/kg do not result in tissue sequestration of the test article or its metabolites. Under the conditions of these experiments, NI-25 is extensively and rapidly metabolized. Metabolites accounted for 79–86% of the administered radioactivity and profiles were similar for males and females and for both single oral and i.v. dosing (ring-label). Only 3–7% of the dose was recovered in the urine and feces as unchanged test article. The initial Phase I biotransformation appears to be demethylation of the parent compound resulting in a major metabolite, IM-2-1 (13–24% of administered, single dosing and 15–20%, repeat dosing). The most abundant metabolite identified in both sexes was 6-chloronicotinic acid, or IC-O (24–28% of dose, single-dose studies and 8–10% of dose, repeat-dose studies), resulting from the removal

of the cyanoacetamide group from demethylated IM-2-1. This removal (and direct removal of the group from NI-25) resulted in the cyanoacetamide metabolites IS-1-1 and IS-2-1, identified in CN-labelled NI-25 single-dose group. Urinary and fecal metabolites from the repeat-dose experiment (Group IV) showed minor differences from the single-dose groups, the most relevant of which was a slight increase (10% of dose, both sexes, vs. <4% in the single-dose groups) in the glycine conjugate of IC-O, indicating induction of metabolic enzymes with repeat exposure.

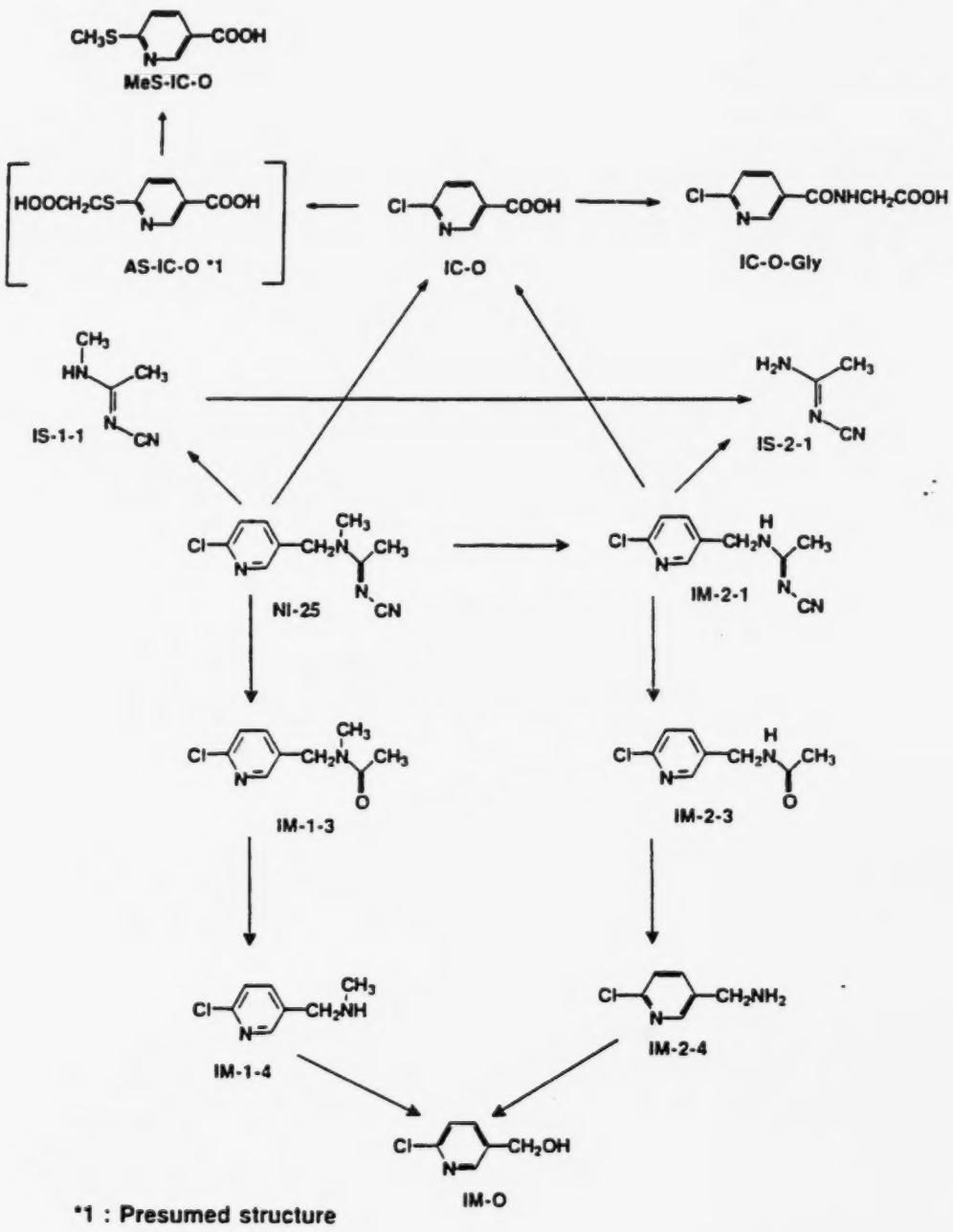


Figure 1. Proposed metabolic pathway for [^{14}C] NI-25 in rats.
Taken from Fig. 3, p. 43, MRID 44988505.

3.1.2 Acute toxicity: technical, metabolites and formulations

Technical acetamiprid, purity 99.5%, was highly toxic to Sprague-Dawley rats via the oral route of exposure. It was of low toxicity to Sprague-Dawley rats via the dermal route of exposure and slightly toxic to Sprague-Dawley rats via the inhalation route of exposure. Technical acetamiprid was minimally irritating to the eye and non-irritating to the skin of New Zealand White (NZW) rabbits. A dermal sensitization study using the guinea pig maximisation method yielded negative results.

Several studies were conducted with metabolites of acetamiprid, all of which indicated that the metabolites were less acutely toxic to Sprague-Dawley rats than the technical material via the oral and (or) dermal routes of exposure.

The formulated product, Assail Brand 70 WP, containing 71.5% acetamiprid, was moderately toxic to Sprague-Dawley rats via the oral route of exposure. It was of low toxicity to NZW rabbits via the dermal route of exposure and it was of low toxicity to Sprague-Dawley rats via the inhalation route of exposure. Assail Brand 70 WP was minimally irritating to the eyes and skin of NZW rabbits. A dermal sensitization study using the Buehler method yielded negative results.

The formulated product, Pristine Brand RTU Insecticide, containing 0.006% acetamiprid, was of low toxicity to Sprague-Dawley rats via the oral and inhalation routes of exposure, low toxicity to NZW rabbits via the dermal route of exposure, minimally irritating to the eyes of NZW rabbits and slightly irritating to the skin of NZW rabbits. A dermal sensitization study using the Buehler method yielded negative results.

3.1.3 Genotoxicity

Technical acetamiprid was tested in a battery of genotoxicity assays. There was no evidence of mutagenic potential in a bacterial reverse gene mutation assay in vitro, in the presence and absence of exogenous metabolic activation. Similarly, a gene mutation assay in Chinese hamster ovary cells in vitro was negative, in the presence and absence of exogenous metabolic activation. There was a weak positive response in the absence of metabolic activation in a chromosomal aberrations assay in vitro, and a dose-dependent positive response in the presence of metabolic activation, indicating that acetamiprid was clastogenic under the conditions of that assay. In an in vivo chromosome aberration assay in Sprague-Dawley rats, acetamiprid showed no evidence of clastogenicity. Acetamiprid did not induce unscheduled DNA synthesis in an assay conducted with cultured primary rat hepatocytes, and the results of the in vivo mouse micronucleus test were negative.

Several studies were conducted with metabolites of acetamiprid to determine their genotoxic potential. Five different metabolites were tested in gene mutation assays in bacteria; all of the test results were negative. One metabolite was tested in a gene mutation assay in cultured mammalian cells and in an in vivo micronucleus assay in mice. Both of these assays yielded negative results. On the basis of the results observed in the

genotoxicity assays with the technical material and its metabolites, the overall conclusion was that acetamiprid is not considered to be genotoxic.

3.1.4 Subchronic and chronic toxicity

The subchronic and chronic toxicity of acetamiprid were investigated in mice, rats and dogs. A series of range-finding 28- and 90-day studies were conducted initially. These studies were used to establish appropriate dose levels to be used in the long-term studies. In addition, a 21-day dermal study was conducted in rabbits.

3.1.4.1 Subchronic and chronic toxicity in the mouse

In a subchronic oral toxicity study (MRID 44988425), groups of Crj:CD-1™ (ICR) mice (10 mice/sex/group) were administered 0, 400, 800, 1600 or 3200 ppm of 31-1359 (Lot No. 591001-7; 99.2% a.i.) in the diet for at least 90 days. Time-weighted average doses were 0, 53.2, 106.1, 211.1 and 430.4 mg/kg/d, respectively, for males and 0, 64.6, 129.4, 249.1 and 466.3 mg/kg/d, respectively, for females.

Treatment related deaths included one 3200-ppm male found dead and another sacrificed moribund during week 12 and two 3200-ppm females that died during weeks 8 and 10, respectively. Clinical signs of toxicity were limited to tremors in 5/10 females in the 3200-ppm group during weeks 4–13. No treatment related clinical signs were observed in males or the remaining treated females.

Absolute body weights, body weight gains, food consumption, and food efficiency of the 400- and 800-ppm males and females were similar to those of the controls throughout the study. Weekly absolute body weights for the 3200-ppm males and females ranged from 65 to 79% and 64 to 77%, respectively, of the control group levels and attained statistical significance beginning at week 1. Overall weight change by the 3200-ppm males and females resulted in a net weight loss by both sexes and was significantly less than that of the controls. Absolute body weights for the 1600-ppm males and females were significantly (82–91% of controls) less than the controls beginning at weeks 3 and 1, respectively. Overall body weight gains by the 1600-ppm males and females were 19 and 21%, respectively, of the control levels.

Males in the 3200 ppm group had significantly (64–75% of controls) reduced weekly food consumption values throughout the study compared with the controls except for weeks 3 and 12. Food consumption by the 3200-ppm females was also significantly (65–73% of controls) less than that of the controls throughout the study. Weekly food efficiencies for the 3200-ppm groups were often negative values and generally less than those of the controls with statistical significance attained at some weeks. Food consumption and food efficiency for the 1600-ppm groups were variable with no consistent patterns.

No treatment related lesions were noted at gross necropsy and no dose related or biologically significant effects were seen on hematology, urinalysis, or ophthalmologic parameters. Hematological parameters were not measured in the 3200-ppm males and females due to marked growth depression and no test article related changes were observed at lower doses.

In the 1600- and 3200-ppm males and females, differences in clinical chemistry parameters, histopathological lesions and organ weights were indicative of inanition. Glucose was significantly decreased compared with the controls for the 1600-ppm males (70% of control) and the 3200-ppm males and females (both 40% of control). Total cholesterol was also decreased in the 1600-ppm females (66% of control) and the 3200-ppm males and females (56 and 52%, respectively, of controls). At 3200 ppm, males and females had significant increases in blood urea nitrogen (BUN) (137 and 178%, respectively), serum glutamate pyruvate transaminase (157 and 233%, respectively) and serum glutamate oxaloacetate transaminase (205 and 180%, respectively) compared with the controls. In the 3200-ppm animals, fat depletion in the adrenal cortex was seen in 4/10 males and 4/8 females.

For the 3200-ppm males, absolute lung, spleen and kidney weights were decreased relative to the control group. Relative (to body weight) mean spleen weight was significantly decreased and relative (to body weight) brain, lung, liver, adrenal and testis weights were significantly increased compared with the control. For the 3200-ppm females, absolute brain, thymus, lung, spleen, kidney, adrenal and ovary weights were significantly less than those of the controls. Also for the 3200-ppm females, significant differences from the controls were noted for increases in relative brain, lung, liver weights and for decreases in relative spleen and ovary weights. At 1600 ppm, significant differences in organ weights included decreased absolute spleen weights for males, increased relative liver and testis weights for males, decreased absolute brain and kidney weights for females, and increased relative liver weights for females. Relative organ weight differences may have been due to lower body weights in treated groups compared with control body weights.

Therefore, the lowest observed adverse effect level (LOAEL) for male and female mice is 1600 ppm (211.1 and 249.1 mg/kg/d, respectively) based on reduced body weights and body weight gains, decreased glucose and cholesterol levels, and reduced absolute organ weights. The no observable adverse effect level (NOAEL) for males and females is 800 ppm (106.1 and 129.4 mg/kg/d, respectively).

In an oncogenicity study (MRID 44988428), acetamiprid (99.7% a.i.) was administered to groups of Crl:CD-1 (ICR) BR mice, 50/sex/dose in the diet at concentrations of 0, 130, 400 or 1200 ppm (0/0, 20.3/25.2, 65.6/75.9, 186.3/214.6 mg/kg body weight (bw)/d in males/females, respectively) for 78 weeks. An additional 10 mice/sex at each dietary concentration were used for interim sacrifice after 52 weeks.

Treatment with acetamiprid had no effect on survival rates compared with the control group. Treatment related clinical signs were limited to decreased defecation in the high-dose male and female groups in the first 13 weeks of the study. There were no treatment related effects on hematology or gross pathology.

In the first year of study, group mean body weight gains were significantly lower than controls for the high-dose males and females but were similar to controls during the second year of study. High-dose males and females had significantly lower absolute body weights throughout the study. There was no difference in the body weights and body weight gains of the low- and mid-dose males and females, and food consumption among these groups were similar to the controls. Food consumption was significantly reduced at 1200 ppm and food efficiency was significantly reduced during the first few weeks of the study.

The incidence of centrilobular hepatocellular hypertrophy was increased among high-dose males and females. There were no other toxicologically significant histopathology findings. Treatment with acetamiprid for up to 78 weeks did not result in a significant increase in the incidence of neoplastic lesions in this study. Under the conditions of this study, acetamiprid was not oncogenic in CD-1 mice.

The LOAEL is 1200 ppm in the diet (186 and 215 mg/kg/d in males and females, respectively) based on decreased body weights, body weight gains and food consumption. The NOAEL is 400 ppm (65.6 and 75.9 mg/kg/d in males and females, respectively).

3.1.4.2 Subchronic and chronic toxicity in the rat

In a subchronic oral toxicity study (MRID 44651843), acetamiprid (>99% a.i.) was administered to groups of 10 Crj:CD (Sprague-Dawley) rats/sex/dose in the diet at dose levels of 0, 50, 100, 200, 800 or 1600 ppm (0, 3.1, 6.0, 12.4, 50.8 and 99.9 mg/kg/d for males, respectively, and 0, 3.7, 7.2, 14.6, 56.0 and 117.1 mg/kg/d for females, respectively) for 13 weeks.

Treatment with acetamiprid induced a dose related reduction of growth rate in males and females as indicated by decreases in body weights, food consumption, food efficiency, and (or) absolute organ weights.

In animals fed 800 ppm acetamiprid, decreases in mean absolute body weights were observed in males from weeks 1–12 (90–92% of controls) and in females during weeks 6–13 (89–90%). During the treatment period, 800-ppm males and females gained 13 and 21% less weight than controls, respectively, resulting in final body weights 91 and 89% of controls, respectively. Decreased food consumption levels (g/animal/d) were observed in 800-ppm males at week 1 (80% of controls) and in 800 ppm females at weeks 1–7, 10, 12 and 13 (80–91% of controls). No statistically significant differences were observed in mean food efficiencies.

In animals fed 1600 ppm acetamiprid, males and females had decreases in mean absolute body weights at each week of treatment (85–87% for males; 77–90% for females), with final mean absolute body weights being 87 and 79% of controls, respectively. Mean body weight gains for the treatment period of weeks 1–13 were 80% and 59% of controls, respectively. Decreased food consumption levels (g/animal/d) were observed in high-dose males during weeks 1–7 (78–91% of controls), and in high-dose females during weeks 1–13 (73–91% of controls). Mean food efficiency was significantly decreased in high-dose males at weeks 1 and 6 (52 and 79% of controls, respectively), and in high-dose females at weeks 1, 3 and 6 (41, 66 and 47% of controls, respectively). High-dose females additionally had changes in organ weights consistent with reduced body weights, including decreased absolute weights of heart (87%), kidneys (87–90%) and adrenals (79–80%), and increased relative weights of brain (126%), lung (123%), heart (113%) and kidneys (112–116%).

Increased levels of total cholesterol were observed in high-dose males (141% of controls) and females (124% of controls). Liver weights relative to body weights were increased in 800 and 1600 ppm males (113 and 126% of controls, respectively) and females (115 and 128% of controls, respectively). Microscopic examination of the liver revealed centrilobular hypertrophy in 10/10 males fed 800 or 1600 ppm and 8/10 and 10/10 females fed 800 or 1600 ppm, respectively, with the mean severity of the lesion graded as 1.8 and 3.0, respectively, for males and 1.0 and 1.9, respectively, for females. This lesion was not observed in any of the other treated animals or in the controls.

The LOAEL for male and female rats is 800 ppm (50.8 and 56.0 mg/kg/d, respectively) based on dose related decreases in body weights, body weight gains, and food consumption. The NOAEL for male and female rats is 200 ppm (12.4 and 14.6 mg/kg/d, respectively).

In a chronic toxicity/oncogenicity study (MRID 44988429 and 45245304), NI-25 (>99% a.i.; Lot No. NNI-01) was administered to groups of 60 male and 60 female Crl:CD® BR rats in the diet at concentrations of 0, 160, 400 and 1000 ppm (0, 7.1, 17.5 and 46.4 mg/kg/d for males and 0, 8.8, 22.6 and 60.0 mg/kg/d for females). Ten rats per sex per dose were sacrificed at 12 months for interim evaluations; the remaining animals were maintained on their respective diets for up to 24 months.

There were no treatment related effects on mortality; eyes; hematology, clinical chemistry or urinalysis parameters; or gross findings in either sex administered any dose of the test material. Clinical signs that were observed at significantly increased incidences in treated animals included rales in high dose males (7/48 vs. 0/46 for controls) during weeks 66–78 and at all doses in males during weeks 79–91 (0/44, 8/49, 19/45 and 17/48 at 0, 160, 400 and 1000 ppm, respectively). Also in high-dose male rats, the incidence of laboured breathing (15/48 vs. 5/46 for controls) was increased during weeks 66–78, red material around the nose during weeks 1–13 (7/60 vs. 0/60 for controls) and weeks 92–104 (5/46 vs. 0/37), and hunched posture (5/46 vs. 0/37) during weeks 92/104.

Treatment related effects on body weight, body weight gain, and food consumption were observed in both sexes. High-dose male rats weighed 10–13% less than controls throughout the study, gained 44% less weight during week 1, 14% less during the first year and 18% less over the entire study. High-dose males also consumed 19% less food (g/animal/d) during week 1 and 4–9% less at different time points during the remaining weeks of the study. Food efficiency measured during the first 14 weeks was reduced for males in all dose groups during the first week of the study and showed an inconsistent pattern for the remaining 13 weeks. Mid-dose female rats weighed 4–17% less than controls throughout the study and high-dose females weighed 6–27% less. Mid- and high-dose females, respectively, gained 27 and 42% less weight than controls during week 1, 15% and 32% less during the first year, and 16% and 23% less over the entire study. Food consumption was 6–10% and 9–19% less for mid- and high-dose females, respectively, for most of the study. Food efficiency was reduced for mid- and high-dose females during week 1 and showed inconsistent patterns for the remaining 13 weeks.

The postmortem examination showed statistically significant changes in absolute and (or) relative weights of several organs in high-dose male and female rats, and these changes are attributed to the decreased terminal body weight. Treatment related microscopic changes were observed in the liver, kidney and mammary glands. Trace to mild hepatocyte hypertrophy in the liver of mid- and high-dose male rats and high-dose group female rats at interim sacrifice and in the main study groups is considered an adaptive response rather than an adverse effect. Hepatocyte vacuolation also was observed in mid- and high-dose group male rats; the incidence was 10/12 and 10/11, respectively, compared with 2/12 for controls at interim sacrifice and 22/48 and 29/48, respectively, compared with 10/48 for controls in the main study. An increased incidence of microconcretions in the kidney papilla was noted for high-dose male rats (37/49 vs. 17/48 for controls) in the main study. The incidence of 24/49 for mammary hyperplasia in high-dose group females compared with 14/49 for controls appeared to be treatment related, but the toxicologic significance of this finding is uncertain as the increase was predominantly of trace severity.

At the doses tested, there was a slight increase in the incidence of mammary adenocarcinoma in females (10/59, 11/60, 16/60 (26.7%) and 17/60 (28.3%) for 0, 160, 400 and 1000 ppm, respectively). The incidence at the mid- and high-dose exceeded that of historical controls at the testing laboratory (14–18%), although it did not attain statistical significance by pairwise comparison. Comparison to historical controls for Charles River Laboratories (9–58%) indicated that the incidence observed in this study was within the range observed in this strain of rat from the supplier. The lack of supporting pre-neoplastic lesions indicates that it is unlikely that this observation is related to treatment with acetamiprid. Dosing was considered adequate based on significantly decreased mean body weight gain when compared with the control groups in both sexes and an increased incidence of hepatocyte vacuolation in male rats.

The LOAEL for NI-25 is 400 ppm (17.5 mg/kg/d for males and 22.6 mg/kg/d for females) for male and female rats based on reduced body weight and body weight gain for females and hepatocellular vacuolation for males. The NOAEL is 160 ppm (7.1 mg/kg/d for males and 8.8 mg/kg/d for females).

Subchronic toxicity studies conducted with Sprague-Dawley rats on two metabolites of acetamiprid indicated that adverse effects of treatment were induced at higher doses than those observed in the studies with the technical material, with no specific indication of unique target organ toxicity.

3.1.4.3 Subchronic toxicity in the dog

In a subchronic toxicity study (MRID 45245306), acetamiprid (99.46% a.i.) was administered to 2 Beagle dogs/sex/dose in the diet at dose levels of 0, 125/3000, 250, 500 and 1000 ppm (equal to 0, 4.1/42.5, 8.4, 16.7 and 28.0 mg/kg bw/d in males and 0, 4.8/46.2, 8.7, 19.1 and 35.8 mg/kg bw/d in females) for 28 days.

Treatment with acetamiprid had no effect on mortality, clinical signs of toxicity, hematology, clinical chemistry and macroscopic pathology. After 2 weeks of treatment, the 125 ppm group dose was increased to 3000 ppm and continued for 4 weeks. Upon initiation of dosing at 3000 ppm, a marked decrease in food consumption was observed. Significant body weight loss was observed at 3000 ppm, and a decrease in body weight gain was observed at 1000 ppm. Slightly reduced absolute and relative (to brain) kidney and liver weights were observed among 3000 ppm animals, which were considered to reflect the observed changes in body weight at that dose.

The LOAEL was 1000 ppm (equal to 28.0 and 35.8 mg/kg bw/d in males and females, respectively), based on the observed reduction in body weight gain in animals of both sexes. The NOAEL was 500 ppm (equal to 16.7 and 19.1 mg/kg bw/d in males and females, respectively).

In a subchronic toxicity study (MRID 44988424), acetamiprid (99.46% a.i.) was administered to 4 Beagle dogs/sex/dose in the diet at dose levels of 0, 320, 800 and 2000 ppm (equal to 0, 13, 32 and 58 mg/kg bw/d in males and 0, 14, 32 and 64 mg/kg bw/d in females) for 90 days.

Treatment with acetamiprid had no effect on mortality, clinical signs of toxicity, ophthalmoscopic examinations, hematology, clinical chemistry, urinalysis, organ weights and macroscopic or microscopic pathology. Group mean body weight and body weight gain was significantly reduced among high dose males and females (animals at this dose lost weight over the course of the study). Decreased body weight gain was observed in males and females at 800 ppm during the first few weeks of the study, such that total gain over the study period was 29% of control in males and 67% of control in females. Decreases in food consumption were consistent with the observed changes in body weight and body weight gain.

The LOAEL was 800 ppm (equal to 32 mg/kg bw/d in males and females), based on the observed reduction in body weight gain in animals of both sexes. The NOAEL was 320 ppm (equal to 13 mg/kg bw/d in males and 14 mg/kg bw/d in females).

In a 1-year toxicity study (MRID 44651846), acetamiprid (99.57% a.i.) was administered to 4 Beagle dogs/sex/dose in the diet at dose levels of 0, 240, 600 and 1500 ppm (equal to 0, 9, 20 and 55 mg/kg bw/d in males and 0, 9, 21 and 61 mg/kg bw/d in females) for 1 year.

Treatment with acetamiprid had no effect on mortality, clinical signs of toxicity, ophthalmology, hematology, clinical chemistry, urinalysis and gross or microscopic pathology. Decreased body weight, body weight gain and food consumption were recorded in high-dose male and female animals. There were no effects of treatment on absolute organ weights nor organ-to-body weight ratios. Significantly decreased kidney-to-brain weight and liver-to-brain weight ratios were attributed to the significant reductions in body weight observed at that dose.

The LOAEL was 1500 ppm (equal to 55 and 61 mg/kg bw/d in males and females, respectively), based on the initial body weight loss and overall reduction in body weight gain in animals of both sexes. The NOAEL was 600 ppm (equal to 20 and 21 mg/kg bw/d in males and females, respectively).

3.1.4.4 Short-term dermal toxicity in the rabbit

In a repeat-dose dermal toxicity study (MRID 44651844), acetamiprid (99.9% a.i.) was applied to the intact shaved skin of 5 NZW rabbits/sex/dose at dose levels of 0, 100, 500 or 1000 mg/kg bw/d, 6 h/d for 5 days/week over a 21-day period.

There were no compound related effects on mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weights, or gross and histologic pathology. The NOAEL is 1000 mg/kg bw/d.

3.1.5 Reproductive and developmental toxicity

3.1.5.1 Developmental toxicity in the rat

In a developmental toxicity study (MRID 44651847), acetamiprid (99.46% a.i.) was administered to 24 female Crj:CD (SD) rats/dose in 5% arabic gum and 0.01% Tween 80 in water, by gavage at dose levels of 0, 5, 16 or 50 mg/kg bw/d from days 6 through 15 of gestation.

There was no mortality, nor were there any clinical signs of toxicity noted in the study. Treatment with acetamiprid did not affect gross pathology nor cesarean section parameters. Maternal body weight, body weight gain and food consumption were reduced at 50 mg/kg bw/d, and absolute and relative liver weights were increased at

50 mg/kg bw/d. The maternal LOAEL is 50 mg/kg bw/d, based on the observed reductions in body weight, body weight gain and food consumption and increased liver weights. The maternal NOAEL is 16 mg/kg bw/d.

Treatment with acetamiprid did not affect the number of fetuses, fetal sex ratios or fetal weights. There were no treatment related changes in fetal external nor visceral examinations. There was an increase in the incidence of the skeletal variation, shortening of the 13th rib, at 50 mg/kg bw/d. The developmental LOAEL is 50 mg/kg bw/d, based on the increased incidence of shortening of the 13th rib. The developmental NOAEL is 16 mg/kg bw/d.

3.1.5.2 Developmental toxicity in the rabbit

In a developmental toxicity study (MRID 44651848), acetamiprid (99.46% a.i.) was administered to 17 female Kbs:NZW rabbits/dose in 5% arabic gum and 0.01% Tween 80 in water, by gavage at dose levels of 0, 7.5, 15 or 30 mg/kg bw/d from days 6 through 18 of gestation.

There were no treatment related mortalities nor clinical signs of toxicity in the study. Six accidental deaths occurred among treated animals; however, these were reported to be due to dosing or handling errors. Maternal food consumption was significantly reduced at 30 mg/kg bw/d on gestation days 6–8, and a slight loss of maternal body weight was recorded among these animals over the interval of gestation days 6–10. There were no other treatment related changes observed among maternal animals.

The NOAEL for maternal toxicity is 15 mg/kg bw/d, based on decreased food consumption and body weight loss at 30 mg/kg bw/d. The maternal LOAEL is 30 mg/kg bw/d.

No signs of developmental toxicity were observed in this study. Treatment with acetamiprid did not affect the number of fetuses, fetal sex ratios or fetal weights. There were no treatment related changes in fetal external, visceral nor skeletal examinations.

The NOAEL for developmental toxicity is 30 mg/kg bw/d, based on the lack of any treatment related changes in any of the parameters investigated in this study.

There was no evidence of any teratogenic effects due to treatment with acetamiprid.

3.1.5.3 Reproductive toxicity in the rat

In a two-generation reproduction study (one litter per generation, MRID 44988430) acetamiprid (99.9% a.i.) was administered to 26 Crl:CD BR (IGS) Sprague-Dawley rats/sex/dose in the diet at dose levels of 0, 100, 280, or 800 ppm (equal to 0, 6.5, 17.9 or 51.0 and 0, 7.6, 21.7 or 60.1 mg/kg bw/d in males and females, respectively).

There were no treatment related mortalities or clinical signs of toxicity among parental animals in either generation. In addition, there were no definitive treatment related clinical signs among F_1 or F_2 pups. In the F_1 parental generation, two 100-ppm females and five 800-ppm dams experienced total litter death. There was an equivocal association with the incidence of thin, pale and (or) weak pups among those litters that experienced total litter death, such that the combined incidence of those clinical signs suggested a possible relationship to treatment with acetamiprid. Mean litter size (day 4 pre-cull), viability index and weaning index were significantly reduced at 800 ppm among F_2 pups. Mean litter size was also reduced among F_1 pups on lactation days 14 and 21.

Body weight, body weight gain and food consumption were reduced during the premating period among males and females at 800 ppm in both generations. A slight, transient, non-adverse reduction in body weight gain and food consumption was observed in males of both generations at 280 ppm for the first few weeks (2–5) on the test diets. Maternal body weight and body weight gain were also reduced during the gestation period; however, body weight gain tended to increase during the lactation period at 800 ppm.

There were no treatment related changes in reproductive function tests, including estrous cycle length and periodicity and sperm motility, count and morphology. Similarly, there were no treatment related changes in reproductive performance in either generation. Decreases in absolute and relative organ weights at 800 ppm were attributed to the observed reduction in body weight among these animals. There were no treatment related macroscopic or microscopic pathology findings in this study.

In addition to the litter size, viability index and weaning index observations noted among offspring, significantly reduced pup weights were observed throughout the lactation period in males and females of both generations at 800 ppm. The mean age to attain vaginal opening was significantly increased for females at 800 ppm and the mean age to attain preputial separation was significantly increased for males at 800 ppm. Eye opening and pinna unfolding were delayed among F_2 offspring at 800 ppm. The observed changes in offspring organ weights are attributable to reductions in body weight at 800 ppm. There were no treatment related macroscopic pathology findings in offspring from either generation.

The LOAEL for parental systemic toxicity was 800 ppm (equal to 51.0 mg/kg bw/d in males and 60.1 mg/kg bw/d in females), based on observed reductions in body weight, body weight gain and food consumption. The NOAEL was 280 ppm (equal to 17.9 mg/kg bw/d in males and 21.7 mg/kg bw/d in females).

The LOAEL for offspring toxicity was 800 ppm (equal to 51.0 mg/kg bw/d in males and 60.1 mg/kg bw/d in females), based on significant reductions pup weights in both generations, reductions in litter size, and viability and weaning indices among F_2 offspring as well as significant delays in the age to attain vaginal opening and preputial separation. The NOAEL was 280 ppm (equal to 17.9 mg/kg bw/d in males and 21.7 mg/kg bw/d in females).

The LOAEL for reproductive toxicity was 800 ppm (equal to 51.0 mg/kg bw/d in males and 60.1 mg/kg bw/d in females), based on observed reductions in litter weights and individual pup weights on the day of delivery (lactation day 0). The NOAEL was 280 ppm (equal to 17.9 mg/kg bw/d in males and 21.7 mg/kg bw/d in females).

3.1.6 Neurotoxicity (acute and subchronic)

3.1.6.1 Acute neurotoxicity in the rat

In an acute neurotoxicity range finding study (MRID 44651841), groups of fasted, male and female Crl:CD-BR rats (3/sex/dose), were given a single oral dose of acetamiprid (99.9% pure) in 0.5% sodium carboxymethylcellulose by gavage, at doses of 10, 50 or 100 mg/kg bw and observed for 14 days.

All animals survived to study termination. A slight decrease in body weight gain was observed in females at 100 mg/kg bw. Body weight was unaffected in males as well as females in the 10 and 50 mg/kg bw dose groups. Clinical signs of toxicity included hind limb tremors in high-dose males, marked tremors in the limbs of high-dose females and dilatation of the pupils in high-dose females.

Functional observation battery (FOB) evaluations revealed a number of treatment related adverse behavioural observations, including reduced body temperature, hunched posture and constant grooming among high-dose males, moderate/marked body tremors, lower body temperature, hunched posture and dilated pupils in high-dose females. In addition, females treated at 50 mg/kg bw exhibited tail tremors and moderate body tremors. There were no clearly treatment related effects at 10 mg/kg bw; however, reduced body temperature was observed at all doses. Due to the small sample size, it is not possible to determine whether this observation is incidental or attributable to treatment with acetamiprid. The maximum signs of toxicity were observed during the FOB conducted 5 h post-dosing.

The author concluded that 100 mg/kg was a reasonable dose to use as the high dose in the acute neurotoxicity study, with a time to peak effect of approximately 5–6 h following dosing.

In an acute neurotoxicity study (MRID 44651842), groups of fasted, male and female Crl:CD-BR rats (10/sex/dose), were given a single oral dose of acetamiprid (99.9%) by gavage, in 0.5% sodium carboxymethylcellulose at doses of 0, 10, 30, or 100 mg/kg bw and observed for 14 days. There were no mortalities during the study. Body weight gain and food consumption were significantly reduced in high-dose males. Body weight, body weight gain, food consumption and food efficiency were unaffected in females. Treatment with acetamiprid had no effect on brain size or weight and there was no evidence of neuropathology. Clinical signs of toxicity were limited to the high-dose animals, and included tremors, hunched posture, unsteady gait and coldness to touch. In addition, one high-dose female had slight brown nasal staining from study day 2 until termination.

High-dose males and females had significantly reduced body temperature on the day of dosing. Significantly decreased motor activity was observed in mid- and high-dose males and in high-dose females on the day of dosing. A slight decrease in the duration of movements persisted in mid- and high-dose males on days 7 and 14. Functional observational battery evaluations revealed several treatment related observations on the day of dosing. High-dose males exhibited tremors, difficulty in handling, walking on toes, dilated pupils and coldness to the touch. High-dose males also had decreased forelimb grip strength and hind limb foot splay. High-dose females displayed tremors, chewing, coldness to the touch and dilated pupils. High-dose females had decreased hind limb foot splay. High-dose females were seen to have abnormal gaits and (or) posture, including walking on toes and hunched posture.

The LOAEL for neurotoxicity was 30 mg/kg bw, based on the observed reduction in locomotor activity in males. The NOAEL for neurotoxicity was 10 mg/kg.

3.1.6.2 Subchronic neurotoxicity in the rat

In a subchronic neurotoxicity study (MRID 44651845), groups of fasted, male and female Crl:CD-BR rats (10/sex/dose), were given daily doses of acetamiprid (99.9%) in the diet for 90 days at doses of 0, 100, 200, 800 and 1600 ppm (equal to 0, 7.4, 14.8, 59.7 and 118 mg/kg bw/d for males and 0, 8.5, 16.3, 67.6 and 134 mg/kg bw/d for females).

There were no mortalities or clinical signs of toxicity recorded during the course of the study. Treatment with acetamiprid had no effect on brain weight, motor activity, behaviour or neuropathology. Body weights, body weight gain, food consumption and food efficiency were reduced in male and female rats at 800 and 1600 ppm.

The LOAEL was 800 ppm (equal to 59.7 and 67.6 mg/kg bw/d for males and females, respectively) based on reductions in body weight, body weight gain, food consumption and food efficiency. The NOAEL was 200 ppm (equal to 14.8 and 16.3 mg/kg bw/d for males and females, respectively).

3.1.7 Special studies

In a special pharmacological study (MRID 44988419), 15 groups of 3–8 male Crj:ICR mice, Crj:CD rats or NZW rabbits were administered single doses of NI-25 (acetamiprid, Lot no. NNI-02, purity 99.4%) by gavage, intraperitoneal injection (i.p.) or i.v. Dose groups were as follows:

(1) 3 mice/dose at 0, 1, 3, 5, 10, 20, 30 or 60 mg/kg (i.p.);
(2) 3 rabbits/dose at 0, 10, 30 or 60 mg/kg (i.v.) for clinical observations of general activity and neurobehavioral parameters up to 48 h postdosing;
(3) 8 mice/dose at 0, 5, 10 or 20 mg/kg (i.p.) for spontaneous locomotor activity and rearing up to 65 min postdosing;

(4) 8 mice/dose at 0, 5, 10 or 20 mg/kg (i.p.) for assessment of sleeping time (duration of abolition of righting reflex) following sodium pentobarbitol treatment at 30 min postdosing;

(5) 8 mice/dose at 0, 5, 10 or 20 mg/kg (i.p.) for assessment of electroshock-induced maximum tonic flexion and convulsions at 30 min postdosing;

(6) 8 mice/dose at 0, 5, 10 or 20 mg/kg (i.p.) for evaluation of acetic acid-induced writhing response at 30 min postdosing;

(7) 8 rats/dose at 0, 5, 10 or 20 mg/kg (i.p.) to assess rectal temperature at 0, 30, 60 and 120 min postdosing;

(8) 8 mice/dose at 0, 5, 10 or 20 mg/kg (i.p.) to assess muscle tone (traction test) at 30-min intervals up to 180 min postdosing;

(9) in vitro experiments using isolated ileum sections from 7 Hartley guinea pigs/treatment level to assess contractile responses at 10^{-6} to 10^{-3} mg/mL in the absence and presence of agonists (10^{-7} g/mL acetylcholine, 10^{-7} g/mL histamine diphosphate, 10^{-4} g/mL barium chloride and 10^{-5} g/mL nicotine tartrate);

(10) 3–4 rabbits/dose at 0, 1, 3 or 10 mg/kg (i.v.) to assess respiratory rate, heart rate and blood pressure up to 30 min postdosing;

(11) 8 mice/dose at 0, 10, 20 or 40 mg/kg (gavage) to assess gastrointestinal motility at 30 min. postdosing;

(12) 8 rats/dose at 0, 5, 10 or 20 mg/kg (i.p.) to assess water and electrolyte balance in urine for 6 h postdosing;

(13) 8 rats/dose at 0, 5, 10 or 20 mg/kg (i.p.) to assess blood coagulation at 30 min postdosing;

(14) 8 rats/dose at 0, 5, 10 or 20 mg/kg (i.p.) to assess hemolytic potential; and

(15) 6 rats/dose at 0, 5, 10 or 20 mg/kg (i.p.) to evaluate plasma cholinesterase activity at 30 min postdosing.

At 20 and 30 mg/kg, the incidences and magnitude of effects in the general activity and behaviour groups increased but were transient (all surviving animals normal by 24 h postdosing) and included decreased alertness, reactivity, spontaneous activity, muscle tone and grip strength; tremors, stagger and depressed reflexes (anal, cutaneous, attitudinal, ipsilatoral flexor, pinna). One mouse in the 30 mg/kg group died at 120 min postdosing. At 60 mg/kg, more pronounced clinical signs were observed and all mice died within 30 min and all rabbits died within 60 min of dosing. At 10 mg/kg, slightly decreased and physiologically irrelevant spontaneous activity and increased vocalization were noted for mice only. Compared with vehicle controls, NI-25 doses of ≤ 5 mg/kg produced no detectable effects in mice and rabbits. Motor activity was sharply diminished in mice at 20 mg/kg i.p.(locomotor activity –67 to –81% below controls and rearing –75 to –96% below controls) by at least 15 min postdosing to at least 65 min postdosing (non-statistically significant decreases at 10 mg/kg were observed but not considered adverse). At 40 mg/kg (gavage), gastrointestinal motility in mice was significantly decreased (about –52% less than controls). At 10^{-3} g/mL, significantly increased rhythmic contractions and relaxation of isolated guinea pig ileum (both $p < 0.01$) and significant inhibition (all $p < 0.01$) of the activity of acetylcholine (45% of control activity), histamine diphosphate (5%), barium chloride (40%) and nicotine tartrate agonists (0%) were observed. These

findings suggested that the test article affected autonomic nervous system/smooth muscle activity via interaction with nicotinic cholinergic receptors as well as H1 histamine receptors. Pentobarbitol sleeping time was significantly increased (+57% above controls) in mice at 20 mg/kg i.p., suggesting that the test article affected cytochrome P-450 mediated processes via its own metabolism or by altering P-450 content or activity. At 20 mg/kg, i.p., a mild antidiuretic effect was observed in rats as determined by statistically significantly decreased urine volume (–29% less than controls) and sodium and chloride concentrations (–46 and –48%, respectively) and slightly (not significantly) elevated potassium concentrations (+13%). Respiratory rates of anaesthetized rabbits were unaffected with an i.v. dose of 1 mg/kg and only minimally and transiently increased at 3 and 10 mg/kg. Heart rate was unaffected at all doses tested (1, 3 and 10 mg/kg) and hypotension was observed that exhibited notable individual variability with no definitive dose–response. Transient, non-statistically significant decreases in writhing response (no. responses in 10 min reduced by 50% at 30 min postdosing) and muscle tone (fewer animals passing traction test: 3/8 and 4/8 at 60 and 90 min postdosing vs. 6/8 and 7/8 controls) were considered possible treatment related effects. The test article did not affect electroshock-induced maximum tonic flexion or convulsions in mice, induce hemolysis or alter coagulation time, body temperature or plasma cholinesterase activity in rats at the doses tested. The results of this study are consistent with other studies showing that acetamiprid mimics the nicotinic properties of acetylcholine. Based on a number of neuromuscular, behavioural and physiological effects of acetamiprid in male mice, under the conditions of this study, a NOAEL of 10 mg/kg (threshold) and LOAEL of 20 mg/kg could be estimated for a single dose by various exposure routes.

Integrated toxicological summary

A detailed review of the toxicological database for the new insecticide acetamiprid (NI-25) was conducted. The database is complete, consisting of the full array of toxicity studies currently required for regulatory purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to this chemical.

Technical acetamiprid was highly acutely toxic via the oral route of exposure, of low toxicity via the dermal route and slightly toxic via the inhalation route of exposure. Clinical signs of neurotoxicity were observed in the acute oral and inhalation toxicity studies. It was minimally irritating to the eye, non-irritating to the skin and was not a dermal sensitizer. Acute toxicity studies with metabolites of acetamiprid indicated that they were either less toxic (oral) or of equal toxicity (dermal) relative to the technical material.

The formulated product Assail Brand 70 WP was moderately toxic via the oral route of exposure and of low toxicity via the dermal and inhalation routes of exposure. They were minimally irritating to the eye and skin and were not dermal sensitizers.

The formulated product, Pristine Brand RTU Insecticide, was of low toxicity via the oral, dermal and inhalation routes of exposure, minimally irritating to the eye, slightly irritating to the skin and was not a dermal sensitizer.

Acetamiprid was rapidly absorbed, widely distributed to the tissues, extensively and rapidly metabolized and rapidly excreted, predominantly in the urine.

In subchronic and chronic toxicity studies, acetamiprid did not elicit any specific target organ toxicity per se. Generalized toxicity was observed in rats, mice and dogs as decreases in body weight, body weight gain, food consumption and (or) food efficiency. Trace to mild centrilobular hepatocellular hypertrophy was observed in the rodent studies, and hepatocellular vacuolation was observed in the rat chronic toxicity study. These liver effects are more likely indicative of a pharmacological effect rather than frank toxicity, and as such were not considered to be adverse. Subchronic toxicity studies were also conducted with several metabolites of acetamiprid. Each of these studies indicated that the technical material induced treatment related adverse effects at lower doses than the metabolites.

There was no evidence of oncogenicity in the mouse oncogenicity study. A slight increase in the incidence of mammary adenocarcinomas was observed among mid- and high-dose females in the rat chronic toxicity and oncogenicity study. However, pairwise comparisons to the concurrent control incidence were not statistically significant, and there was a lack of a dose–response. The incidence of mammary adenocarcinoma among mid- and high-dose females exceeded the range observed among in-house historical control animals; however, limited data are available; only three studies were conducted by the dietary route. Comparison to the incidence rates of mammary adenocarcinoma in Sprague-Dawley rats from Charles River Laboratories indicates that the incidence is well within the background range of values. In addition, the non-neoplastic mammary pathology observed in this study is not supportive of the tumour incidence being a treatment related effect. An increase in the incidence of mammary gland hyperplasia (trace) was observed among high-dose females; however, this observation was within the range observed among historical controls, and there was no difference between treated and control animals at the mid-dose level.

The U.S. EPA Office of Pesticide Programs Cancer Assessment Review Committee met to discuss the carcinogenic potential of acetamiprid and concluded that it was not likely to be carcinogenic to humans.

Acetamiprid was tested in a battery of genotoxicity studies. Bacterial gene mutation assays were negative, as was an in vitro forward mutation assay in Chinese hamster ovary cells. Acetamiprid was negative in a mouse micronucleus assay as well as in repeat assays for unscheduled DNA synthesis in primary rat liver cell cultures. A positive response was observed in an in vitro mammalian chromosome aberration assay in Chinese hamster ovary cells; however, an in vivo chromosome aberration assay with Sprague-Dawley rats showed no evidence of clastogenicity.

Several studies were conducted with metabolites of acetamiprid to determine their genotoxic potential. Five different metabolites were tested in gene mutation assays in bacteria; all of the test results were negative. One metabolite was tested in a gene mutation assay in cultured mammalian cells and in an in vivo micronucleus assay in mice. Both of these assays yielded negative results. On the basis of the results observed in the genotoxicity assays with the technical material and its metabolites, the overall conclusion was that acetamiprid is not considered to be genotoxic.

There was no evidence of teratogenicity in the developmental toxicity studies, nor was there any evidence of increased susceptibility of the young. As in the subchronic toxicity studies, general toxicity was observed in the dams, as decreased body weight, body weight gain and food consumption. In rats, there was a slight increase in the incidence of a skeletal variation, shortening of the 13th rib, at the highest dose tested. There were no treatment related changes in developmental parameters in the rabbit study.

There was qualitative evidence of increased susceptibility in offspring in the two-generation reproductive toxicity study. Although the NOAELs and LOAELs were the same in parental animals and pups, certain effects in the pups were considered to be more severe than those observed in the parental animals. Generalized toxicity was observed in parental animals as decreases in body weight, body weight gain and food consumption, whereas among pups, the observed effects included decreased pup weights in both generations, decreased litter size, decreased viability and weaning indices among F_2 pups and delays in the age to attain vaginal opening and preputial separation. The litter size, viability index and weaning index observations were restricted to F_2 pups; these observations are considered more severe than those related to growth and development.

In acute and subchronic neurotoxicity studies, treatment with acetamiprid did not result in any neuropathology. In the acute study, reduced locomotor activity, reduced body temperature and functional observational battery effects were observed on the day of dosing, with a slight decrease in the duration of movements persisting throughout the 14-day observation period. In the subchronic study, generalized toxicity was observed as decreased body weight, body weight gain, food consumption and food efficiency. A developmental neurotoxicity study was suggested upon preliminary review of the data; the results of this study should be submitted when the final report is available.

3.2 Determination of acceptable daily intake

The recommended acceptable daily intake (ADI) for acetamiprid is 0.0023 mg/kg bw/d. The most appropriate study for selection of a toxicity end point for chronic dietary exposure was the chronic toxicity and oncogenicity study in rats, with a NOAEL of 7.1 mg/kg bw/d, based on decreased body weight, body weight gain and food consumption. The standard uncertainty factor (UF) of 100 is applied to account for intraspecies and interspecies variability. A developmental neurotoxicity study is not available; however, correspondence from the applicant indicates that it has been initiated. There is qualitative evidence of increased susceptibility of the young in the

two-generation reproduction study, where more severe effects were observed in offspring at the same LOAEL as in the parental animals. Therefore, an additional safety factor (SF) of 3 is applied.

3.3 Acute reference dose

The recommended acute reference dose (ARfD) for acetamiprid is 0.1 mg/kg bw/d. The most appropriate study for selection of a toxicity end point for acute dietary exposure was the acute neurotoxicity study in rats, with a NOAEL of 10 mg/kg bw/d, based on an observed reduction in locomotor activity at 30 mg/kg bw/d. The additional SF of 3 is not required for acute dietary end points. The effects noted in the two-generation reproduction study that were indicative of increased qualitative susceptibility among offspring required prolonged exposure to be observed, therefore the additional SF is not applied to acute dietary exposure scenarios.

Although the NOAEL used in determining the ARfD is lower than the NOAEL used in short- and intermediate-term occupational risk assessments, it is believed that this situation is strictly an artefact of dose selection in the various studies that comprise the toxicity database for this chemical.

3.4 Toxicological end point selection for occupational and bystander risk assessment

For short- and intermediate-term occupational exposures via the dermal and inhalation routes, the NOAEL of 17.9 mg/kg bw/d from the rat reproductive toxicity study was selected. Offspring toxicity was observed in the reproductive toxicity study, including decreased pup weights in both generations, decreased litter size, viability and weaning indices among F_2 offspring and significant delays in the age to attain developmental landmarks (vaginal opening and preputial separation). A 30% dermal absorption factor is recommended for route-to-route extrapolation, whereas 100% absorption is assumed for inhalation exposures. The additional SF is not applied to short- and intermediate-term occupational exposures because the effects that were deemed to be suggestive of qualitative sensitivity among offspring were only apparent in the 2nd generation, indicating the requirement for prolonged exposure to the product to be observed. Therefore, the target margin of exposure (MOE) for these scenarios is 100.

For chronic occupational exposures via the dermal and inhalation routes, the NOAEL of 7.1 mg/kg bw/d from the rat chronic toxicity and oncogenicity study was selected. This study was selected in determining the ADI, and is relevant to chronic exposures via all routes. A 30% dermal absorption factor is recommended for route-to-route extrapolation, whereas 100% absorption is assumed for inhalation exposures. The additional SF noted above is relevant to chronic exposure scenarios, therefore the target MOE for chronic occupational exposure scenarios is 300.

For residential exposures, the NOAEL of 17.9 mg/kg bw/d from the rat reproductive toxicity study was selected. The target MOE is 300.

3.5 Impact on human and animal health arising from exposure to the active substance or to impurities contained in it

Dermal absorption

The dermal absorption of NI-25 (Acetamiprid) was determined in male rats at doses of 1.09, 9.53 and 90.2 $\mu g/cm^2$. Exposure durations were 0.5, 1, 2, 4, 10 and 24 h, four rats per dose duration. Mass balance ranged from 96.6 to 102% of dose.

Absorption increased with duration of exposure. The quantity absorbed increased with dose but the percent absorbed increased between the low and intermediate doses and decreased between the intermediate and high doses. The study design did not permit analysis of the fate of skin bound residues, as such, residues retained at the skin site were added to the dermal absorption value. This is consistent with guidance provided in U.S. EPA Health Effects Test Guidelines OPPTS 870.7600 (Dermal Penetration). The dermal absorption value of 6.34% from the 24-h exposure, 9.53 $\mu g/cm^2$ dose group was selected because it is the highest value in the study. The residue remaining in the skin at 24 h for the 9.53 $\mu g/cm^2$ dose group is 25.0% of the dose. Therefore, the potential total absorption is approximately 30%.

3.5.1 Operators

Foliar uses: Assail Brand 70 WP and Chipco Brand Tristar 70 WSP
Assail Brand 70 WP is a wettable powder formulation containing 70% acetamiprid proposed for use on leafy vegetables, cole crops, fruiting vegetables, pome fruits and grapes. Application would be by ground equipment (i.e., ground boom or airblast) only. Application rates range from 28 to 168 g a.i./ha (see Appendix VI, Value summary). For leafy vegetables and cole crops, a maximum of five applications per season, no more than once every 7 days, is proposed. For fruiting vegetables and pome fruits, a maximum of four applications per season, no more than once every 7 days, is proposed. For grapes, a maximum of two applications per season, no more than once every 14 days, is proposed. For all crops, a preharvest interval of 7 days is identified on the draft label.

Chipco Brand Tristar 70 WSP is a wettable powder formulation containing 70% acetamiprid packaged in water soluble packages. It is proposed for commercial use as a foliar spray to ornamentals and flowering plants grown outdoors and in greenhouses, shadehouses and lathhouses. The product would be applied to bedding plants, flowers grown for cuttings, foliage plants, potted flowering plants, ornamental trees and non-bearing fruit and nut trees. The application rate is 2.5–10 packs/1000 L (28–112 g a.i./1000 L) (see Appendix VI, Value summary). A maximum of five applications per year for outdoor ornamentals and two applications per year for ornamentals grown in shadehouses, lathhouses and greenhouses at a minimum spray interval of once every 7 days is proposed.

The draft label specifies that handlers wear long-sleeved shirt and long pants, waterproof gloves, shoes plus socks and chemical resistant headgear for overhead exposure. No reentry interval is specified.

Based on the number of seasonal applications indicated on the product labels, and information provided by the registrant, mixer/loader/applicator exposure is expected to be short- and intermediate-term in duration for all proposed uses of Assail and Chipco.

Mixer/loader/applicator exposure for foliar uses
Exposure for mixing, loading and applying acetamiprid was estimated using the Pesticide Handlers Exposure Database (PHED) Version 1.1. PHED is a compilation of generic mixer/loader applicator passive dosimetry data with associated software that facilitates the generation of scenario-specific exposure estimates. The PHED estimates meet criteria for data quality, specificity and quantity outlined under the North American Free Trade Agreement Technical Working Group on Pesticides.

To estimate exposure for each use scenario, appropriate subsets of A, B and sometimes C grade data were created from the mixer/loader and applicator database files of PHED. All data were normalized for kg of active ingredient handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part. The exposure estimates are based on the maximum application rate, typical area treated per day, and workers wearing one layer of clothing, no gloves.

The exposure estimates and MOEs for mixing/loading/applying Assail or Chipco are presented in Appendix II, Table 1. The MOEs were calculated from the combined dermal and inhalation exposure from mixing, loading and applying acetamiprid.

The MOEs for mixer/loader/applicator exposure are greater than 100 and, therefore, are acceptable for all proposed uses of Assail and Chipco.

3.5.2 Workers

Foliar uses: Assail Brand 70 WP and Chipco Brand Tristar 70 WSP
Postapplication exposure may occur during re-entry activities in treated crops. Re-entry activities include: hand harvesting, pruning, thinning, irrigation, hand weeding, staking, scouting, topping and tying.

Based on the number of applications indicated on the product labels, postapplication exposure is expected to be short- and intermediate-term in duration for all proposed uses of Assail and Chipco.

Appendix II, Table 2 outlines exposure estimates for workers entering crops that had been treated with the maximum number of applications, applied at the minimum spray interval as recommended on the draft labels. Exposure estimates were based on the following

assumptions: on the day of application 20% of the application rate is available as dislodgeable residue, and the duration of exposure is assumed to be 8 h per day. For outdoor crops, a daily dissipation rate of 10% was assumed. However, for ornamentals grown in greenhouses, shadehouses or lathhouses, there is no default dissipation rate. In the absence of data, it is assumed that there is no chemical dissipation in greenhouses, shadehouses and lathhouses.

The MOEs for activities with the highest exposure potential are acceptable on the day of the last application (≥ 100) for all proposed uses of Assail and Chipco.

3.5.3 Residential

Pristine Brand RTU
Pristine Brand RTU is an RTU liquid foliar spray proposed for Domestic registration. The product contains 0.006% (0.06 g/L) acetamiprid, packaged in a 1 L fibre container lined with polyethylene.

The "Directions for Use" on the label specify direct spraying to upper and lower leaf surfaces and stems where pests appear on flowers and ornamental plants, leafy vegetables and cole crops, fruiting vegetables and pome fruits. The product would not be applied more than once every 7 days, up to a maximum of five applications per season (see Appendix VI, Value summary). A 7-day preharvest interval is specified for food uses. Exposure to applicators would be short-term to intermediate-term in duration.

Applicator exposure was estimated using (1) a trigger pump spray surrogate study and (2) PHED Version 1.1.

Applicator exposure study
The data collected reflect the dermal and respiratory exposure of homeowners applying RP-2 Liquid (21%), a carbaryl end-use product, in a RTU trigger sprayer.

Applications were made by volunteers to two 18-foot rows of tomatoes and one 18-foot row of cucumbers in Florida. Exposure was monitored using inner and outer whole body dosimeters, personal air sampling pumps, face and neck wipes and hand washes. Each replicate opened the end-use product and applied it to the vegetable rows. There were a total of 40 replicates. Inhalation exposure was monitored with personal air sampling pumps with OVS tubes attached to the shirt collar in the breathing zone. Dermal exposure was assessed by extraction of carbaryl from inner and outer 100% cotton dosimeters, face and neck wipes, and glove and hand washes. The inner and outer dosimeters were segmented into: lower and upper arms, lower and upper legs, and front and back torso.

Dermal exposure was determined by adding the values from the bare hand rinses and face and neck wipes to the outer dosimeter lower legs and lower arms plus the inner dosimeter front and rear torso, upper legs and upper arms to represent exposure to residential applicators wearing short-sleeved shirt and short pants.

Pesticide Handlers Exposure Database

To estimate applicator exposure to Pristine, appropriate subsets of A, B and C (dermal only) grade data were created from the aerosol application database files of PHED. All data were normalized for kilogram of active ingredient handled. Exposure estimates are presented on the basis of the best-fit measure of central tendency, i.e., summing the measure of central tendency for each body part that is most appropriate to the distribution of data for that body part. The clothing scenario considered most appropriate for domestic application to outdoor gardens was short pants, short sleeves and no gloves.

Risk assessment

The short- and intermediate-term risk calculations for residential acetamiprid handlers are summarized in Appendix II, Table 3. The exposure estimates are based on one container (0.06 g a.i.) being applied. The MOEs for both methods of estimating exposure (handlers using PHED data for aerosol spray and surrogate data for trigger pump spray) are considered acceptable (≥300).

3.5.4 Bystander

Pristine Brand RTU

There is the potential for postapplication exposure from re-entry activities in home vegetable gardens, ornamentals, grapes and fruit trees that have been treated with Pristine Brand RTU. Re-entry activities include: hand harvesting, pruning, thinning, irrigation, hand weeding, staking, topping and tying. Both adults and children of varying ages can potentially be exposed dermally from these activities.

Postapplication exposures were calculated using the following data and assumptions: on the day of application 20% of the application rate is available as dislodgeable residue; adults weigh 60 kg and youth weigh 39 kg; the duration of exposure is 0.67 h (40 min) per day for adults and youth; and the total area that could be treated with one container is 18.6 m^2.

Pristine Brand RTU may be applied every 7 days up to a maximum of five applications. There is the potential for the accumulation of acetamiprid on foliage, resulting in a potential increase in postapplication exposure after multiple applications. In the absence of chemical-specific dislodgeable foliar residue data, a daily dissipation rate of 10% was assumed for estimating exposure after the maximum number of applications had been applied at the minimal spray interval. After five applications of Pristine Brand RTU at a 7-day interval, MOEs were acceptable (≥300) for youth and adults conducting high exposure activities (see Appendix II, Table 4).

4.0 Residues

The petitioner has submitted **plant metabolism** studies for acetamiprid in or on carrot, cabbage, cotton, apple and eggplant. In addition, a **confined crop rotation** study was submitted. The test compound for these studies was [^{14}C] acetamiprid labelled in the 2 and 6 positions of the pyridine ring.

In the **carrot metabolism** study, extraction procedures released the bulk of the total radioactive residue (TRR) in both carrot tops and roots at the interim and final collection time points. Based on the weight ratio of peel and flesh, the petitioner calculated the total TRR in the extractable (79.36% TRR) and nonextractable (20.64% TRR) fractions for carrot root. Separation and identification of the residues isolated from each fraction was carried out by HPLC and UV (260 nm) detection and radiodetection. Radioactive residues were identified by co-chromatography with non labelled reference standards of acetamiprid and metabolites. Liquid chromatography – mass spectrometry (LC–MS) analyses (electrospray ionization in the positive ion mode) and LC–MS–MS analyses (for metabolite IC-0, thermospray ionization) were used to confirm the identification of the following compounds in 14-day preharvest interval (PHI) commodities: acetamiprid in tops, peel and flesh; IM-1-4 in tops; IM-2-1 in tops and peel; IM-0-GLC in tops and peel; and IC-0 in peel. The results showed that parent was the major component in (weighted) carrot flesh. 32% of the TRR was identified as parent. IC-O (6-chloronicotinic acid) was also observed as a major metabolite (25.8% of the TRR) in carrot.

Both the PMRA and the EPA concluded that the **cabbage metabolism** study was acceptable. Extraction procedures released 61.3–96.4% TRR in soil treated cabbage leaves and roots; extraction was most successful in 7-day PHI leaves and roots, and least successful in 28-day PHI samples. Unextractable residues accounted for 0.8–25.6% TRR following extraction and partitioning procedures. Overall accountabilities ranged from 72.4% TRR in 28-day PHI cabbage leaf to 97.2% TRR in 7-day PHI cabbage leaf. Extracts and eluates of cabbage leaf, head, and root (soil treated only) were analyzed by thin-layer chromatograph (TLC) on three systems. Radioactive residues were identified by co-chromatography with reference standards. Identification of acetamiprid and metabolites was confirmed by LC–MS analysis (thermospray ionization in the positive ion mode); extracts of cabbage commodities from all sampling intervals were pooled for these analyses. LC–MS analyses were used to confirm the identification of the various metabolites in different fractions. In both the foliar applied and soil applied studies, the majority (>60% of the TRR) of the residue identified was parent. Little qualitative differences were observed in the metabolic profile when acetamiprid was applied either as a foliar application or as a soil applied insecticide.

Extraction procedures used in the **cotton metabolism** study released 61.8–97.2% TRR in cottonseed and gin trash; extraction was most successful in 28-day gin trash and least successful in 28-day cottonseed. Unextractable residues accounted for 6.4–21.5% TRR following initial extraction procedures; subsequent enzyme, acid, and base hydrolyses released the majority of bound residues, leaving 0.8–1.7% total unextractable residues in

cottonseed and gin. Overall accountabilities ranged from 77.3% TRR in 28-day gin trash to 94.2% TRR in 14-day cottonseed. Extracts and hydrolysates of cottonseed and gin trash were analyzed by HPLC on three systems. Radioactive residues were identified by co-chromatography with nonlabelled reference standards of acetamiprid and metabolites. Identification of acetamiprid and metabolites was confirmed by HPLC–MS and HPLC–MS–MS analysis in multiple reaction monitoring mode. Following foliar application of the active ingredient, acetamiprid was present in cottonseed at low levels (3.1–4.9% TRR); however, the major residue in cottonseed was the metabolite IC-O (24.2–45.7% TRR).

Although the sampling protocol used in the **apple metabolism and translocation** study was not standard, and the application rates used were much less than the proposed on field use, the PMRA concluded that the results were of sufficient quality to provide a qualitative and quantitative overview of the metabolism of this chemical in apples. Surface washings of the 0- to 90-day PHI treated leaves contained 37.17–99.89% TRR. TRR in surface washings decreased with increasing PHI. A large portion of the remaining radioactivity was extracted with methanol:water (25.36–58.09% TRR). Surface washings, DCM extracts and methanol eluates of apple leaf and fruit were analyzed by TLC on three systems. Radioactive residues were identified by co-chromatography with the following nonlabelled reference standards. HPLC analyses were conducted to confirm metabolite identification with the surface wash, DCM extract and methanol eluate of 90-day PHI leaf and 62-day PHI fruit. Identification of acetamiprid and metabolites was confirmed by LC–MS (thermospray ionization in the positive ion mode) analyses; the identification of acetamiprid and IM-0-Glc in 90-day PHI leaf and acetamiprid and IM-1-3 in 62-day PHI fruit were confirmed by LC–MS. The polar metabolites of the methanol eluate of 90-day leaves and 62-day fruit (peel) were collected, subjected to enzyme hydrolyses in attempts to identify the aglycones and (or) exocones.

Though the sampling protocol used in the **eggplant metabolism** study was unusual, the study was acceptable. Overall accountability for characterization and identification procedures in the study was good; accountabilities were 99.5% TRR for direct foliar treated eggplant leaf and 98.1–99.4% for treated eggplant fruit. We note that no metabolism through IM-1-3 was observed in this crop.

General conclusion regarding the plant metabolism for target crops: parent acetamiprid is the predominant residue (>90% TRR) in three of the five metabolism studies. Although metabolite IC-O is a major metabolite in cotton seed (24% TRR) and carrot flesh (31% TRR), toxicological data indicate that IC-O is not a compound of concern and should not be included in the risk assessment or the tolerance and maximum residue level (MRL) expression. We also noted that IC-O was not unique to acetamiprid and therefore could not serve as a regulatory marker. For both the risk assessment and tolerance expression, the residue of concern (ROC) is acetamiprid, per se. Due to the definition of the ROC, the potentially quantitative differences in the metabolic pathway that appears to occur in eggplant was not of concern.

The PMRA reached the following conclusions regarding the **confined rotation** studies. The major metabolite in rotational crops, IM-1-4, was also observed, directly or indirectly, in cotton, apple, carrot and cabbage (not eggplant) metabolism studies. This metabolite was the primary soil metabolite. In addition, metabolite IC-O and its glycoform (IC-O-Glc) was also observed in four of the metabolism studies carried out on primary crops (apple, carrot, cabbage and eggplant, not cotton).

The **animal metabolism** studies are classified acceptable and do satisfy the guideline requirements for livestock metabolism studies pending the submission of quantitative raw data needed to support the reported TRR and metabolite residue values.

The metabolic profile of acetamiprid observed in **laying hens** was similar to the metabolic profile observed in goat and rat. The metabolism of acetamiprid proceeded through an initial N-demethylation of the parent with subsequent sequential cleavage of the cyano-methylacetamidine moiety. Briefly, the accountability of the dose and extractability of the TRR was high for all matrices. Greater than 93% of the administered dose was excreted in the feces. The metabolites were separated, identified and quantitated by multiple methods. Extracts were analyzed using TLC, HPLC and (or) LC–MS. Nonlabelled compounds were visualized under UV light. The following nonlabelled reference compounds were used: acetamiprid, IM-1-2, IM-1-3, IM-1-4, IC-O, IM-O, IM-O-GLC, IM-2-1, IM-2-3 and IM-2-4. Metabolites were identified by co-chromatography and (or) by comparison of Rf values. HPLC was used to confirm metabolite identification. HPLC was used to confirm the identification of the following metabolites (by co-chromatography): IM-2-1 and IM-2-3 in all matrices from high-dose hens; IM-2-4 in egg yolk (120–144 h) from high-dose hens; and IC-O in skin from high-dose hens. LC–MS analyses were conducted. The MS was operated in atmospheric pressure chemical ionization (APCI) mode (positive or negative). LC–MS analyses were used to further confirm the identification of IM-2-1 in all matrices from high-dose hens, and IM-2-3 in egg whites and yolks, muscle and skin from high-dose hens. The identification of IC-O in skin (high dose) was confirmed by GC–MS (DB-1701 column, full scan MS). TLC analysis of the aqueous phase of egg yolk (high dose, 312–336 h) resolved three fractions: IM-2-4 and two unknowns (Y5 and Y6). Following acid hydrolysis of the aqueous phase, unknown Y6 was not observed and IM-2-4 and unknown Y5 were found to be resistant to hydrolysis. The petitioner isolated fraction Y5 (from high-dose egg yolk using HPLC with fraction collection) and subjected it to LC–MS analyses. These analyses indicated that Y5 is IM-2-3-imine, which the petitioner named IM-2-5. IM-2-5 appears to be a unique metabolite to the hen that is observed in egg yolks accounting for up to 26% of the total terminal residue (0.241 ppm) in the high dose (102× theoretical maximum dietary burden).

The metabolic profile of acetamiprid observed in **lactating goat** was similar to the metabolic profile observed in laying hen and rat. The metabolism of acetamiprid proceeded through an initial N-demethylation of the parent with subsequent sequential cleavage of the cyano-methylacetamidine moiety. Overall accountability of the dose and extraction of the TRR were excellent. The TRR was separated and identified using TLC,

HPLC and (or) LC–MS. Metabolites were identified by co-chromatography and (or) by comparison of Rf values. Radioactive zones on TLC pates were detected using a TLC linear analyzer; zones were quantified using the Gaussian fit method. HPLC was used to confirm metabolite identification. HPLC was used to confirm the identification of the following metabolites (by co-chromatography): acetamiprid and IM-2-1 in milk from Goat 2; IM-2-1 in liver from Goat 2; IM-2-1 and IC-O in kidney from Goat 2; and IM-2-1, IM-2-3, and IM-2-4 in muscle from Goat 2. LC–MS analyses were conducted using a Kromasil 100 C18 column and a gradient mobile phase of ACN and ammonium acetate buffer, an MS detector, and a radiodetector. The MS was operated in APCI ionization mode (positive or negative). LC–MS was used to further confirm the identification of IM-2-1 in the milk, liver, kidney, and muscle of Goat 2. Acetamiprid and metabolite IM-2-1 are the major residues in all ruminant tissues except muscle, where IM-2-1-amide accounts for nearly 50% of the TRR. IM-2-1-amide was not found in any other ruminant tissue. Metabolite IM-2-1 is the major residue in poultry tissues and eggs (50–80% TRR). IM-2-5 is also a major residue in eggs (~20% TRR). Parent acetamiprid was not detected in poultry tissues or eggs.

Available toxicological data and structural similarity indicated that both IM-2-1 and IM-2-1-amide have toxicity comparable to that of acetamiprid. IM-2-5 is expected to be less toxic than IM-2-1. The residues of concern for both risk assessment and regulatory purposes in livestock commodities are parent acetamiprid and IM-2-1. Residues of IM-2-1-amide in ruminant muscle should also be included for purposes of risk assessment. IM-2-5 does not need to be included in either the ROC or the risk assessment. Potential effects of IM-2-5 are considered to be covered by inclusion of IM-2-1.

Multiple residue trials were carried out in the representative crops of crop group 4: celery, lettuce and spinach. All of these trials were carried out in multiple U.S. zones some of which are common to Canadian zones. All of the trials submitted in support of an MRL on this crop group were carried out at 1.4× the maximum sustainable rate. The results from the U.S. trials are summarized below. In celery, the MRL observed was 0.780 ppm. In head lettuce, the MRL observed was 0.743 ppm in or on head lettuce with wrapper leaves and 0.294 ppm in head lettuce without wrapper leaves. The results from the leaf lettuce trials indicated that the MRL observed was 1.07 ppm. In spinach, the MRL observed was 2.58 ppm.

The results from trials conducted in zones applicable to Canada carried out at the same application rate as those in unique U.S. zones have shown that the MRLs observed are lower in zones applicable to Canada. For head and leaf lettuce, the highest residue level observed was 0.18 ppm (0.743 ppm in the U.S.). In trials carried out in spinach, the residue observed in Canadian zones were 0.23 ppm (2.58 ppm in U.S.). No residue trials in celery were carried out in zones applicable to Canada.

For the **leafy vegetables group**, the number and location of the trials satisfies the U.S. guideline requirement for crop field trials however, the number and location of the trials submitted does not satisfy the requirements set out in the Canadian *Residue Chemistry Guidelines* (DIR98-02, Section 9). In addition to the zonal deficiencies, the PMRA notes that the trials were carried at 1.4× the rate supported by efficacy. We note, however, that MRLs reported for acetamiprid residues in Canadian lettuce and spinach trials were 6–11× lower than the MRLs in U.S. lettuce and spinach trials. Due to the high quality of the data submitted as well as the residue profile observed, the PMRA has decided to grant the registrant partial relief from the full requirements of the residue chemistry guidelines. Consequently, the PMRA will only require one additional trial for lettuce from zone 5B and two additional trial carried out in zone 5B on celery as a condition of the Canadian registration.

Based on the available residue data for the representative crops of the leafy vegetable group, a crop group MRL of 3.0 ppm is recommended.

Multiple residue trials were carried out in the representative crops of crop group 5: broccoli, cabbage and mustard greens. All of these trials were carried out in multiple U.S. zones some of which are common to Canadian zones. All of the trials submitted in support of an MRL on this crop group were carried out at 1× the maximum sustainable rate. The results from the U.S. trials are summarized below. The results from the supervised crop field trials in broccoli have shown that the MRL was 0.25 ppm. In cabbage the MRLs in cabbage were 0.50 ppm in or on cabbage with wrapper leaves and 0.05 ppm in or on cabbage without wrapper leaves. Results from the trials in mustard greens have shown that the MRL in mustard greens was 1.1 ppm.

The results from trials conducted in zones applicable to Canada carried out at the same application rate as those in unique U.S. zones have shown that the MRLs observed are lower in zones applicable to Canada. For broccoli, the highest residue level observed was 0.1ppm (0.25 ppm in the U.S.). In trials carried out in cabbage, the residues observed in Canadian zones were 0.011 and 0.027 ppm for cabbage with and without wrapper leaves (0.5 and 0.05 ppm in the U.S. for cabbage with and without wrapper leaves). No residue trials in mustard greens were carried out in zones applicable to Canada.

The number and location of the trials satisfy the U.S. guideline requirement for crop field trials; however, the number and location of the trials submitted does not satisfy the requirements set out in Dir98-02, Section 9. We note that, with respect to establishment of a Canadian MRL based on shared U.S. and Canada data, MRLs reported for acetamiprid residues in the Canadian broccoli and cabbage trials were generally lower than the MRLs in the U.S. broccoli and cabbage trials. Due to the high quality of the data submitted, the PMRA has decided to grant the registrant partial relief from the full requirements of the residue chemistry guidelines. Consequently, the PMRA will only require one additional trial for broccoli and cabbage carried out in zone 5B as a condition of registration.

Based on the available data for broccoli, cabbage and mustard greens, a crop group MRL of 1.2 ppm would be adequate to cover residues of acetamiprid in the brassica (cole) leafy vegetables group, crop group 5.

Multiple residue trials were carried out in the representative crops of crop group 8: tomato and peppers. In addition, the registrant has submitted residue trials in eggplants in support of the proposed crop group MRL. All of these trials were carried out in multiple U.S. zones some of which are common to Canadian zones. All of the trials submitted in support of an MRL on this crop group were carried out at 1× the maximum sustainable rate. The results from the U.S. trials are summarized below. The results from the supervised crop field trials in tomato have shown that the MRL was 0.11 ppm. In bell and non-bell pepper, the MRLs were 0.09 and 0.16 ppm, respectively. Results from the trials in eggplant trials showed that the MRL was 0.05 ppm.

The U.S. EPA has concluded that the supervised crop field trials for fruiting vegetables are acceptable however an insufficient number of residue trials were carried in zones applicable to Canada to support a domestic registration on the fruiting vegetable crop group. As there are few trials in common zones, the PMRA cannot consider a domestic registration on crop group 8 based on the trials number of trials submitted. A temporary domestic registration on tomatoes as a single commodity can however be supported pending the submission of five additional trial in or on tomatoes distributed as follows: four additional trials from zone 5 and one additional trial carried in zone 5B. The PMRA will however recommend an MRL to cover the residues of acetamiprid in or on domestically produced tomatoes and to facilitate the import of other fruiting vegetables from the U.S.

Based on the available data for eggplants, peppers and tomatoes, a crop group MRL of 0.2 ppm is recommended to match the crop group tolerance proposed by the U.S.-EPA to cover residues of acetamiprid in the fruiting vegetables (except cucurbits) group, crop group 8.

The results from the supervised crop field trials in the citrus crop group have shown that the MRLs observed in the representative crops were as follows: oranges, 0.29 ppm; grapefruit, 0.27 ppm; and lemon, 0.39 ppm.

Based on the available data for grapefruit, lemons and oranges, a crop group MRL of 0.5 ppm would be adequate to cover residues of acetamiprid in the citrus fruits group, crop group 10.

Multiple residue trials were carried out in the representative crops of crop group 11: apples and pears. All of these trials were carried out in multiple U.S. zones some of which are common to Canadian zones. All of the trials submitted in support of an MRL on this crop group were carried out at 1× the maximum sustainable rate. The results from the U.S. trials are summarized below. The results from the supervised crop field trials in apples have shown that the MRL was 0.64 ppm. In pears, the MRLs was 0.36 ppm.

Residue decline data submitted from one trial indicate that residues of acetamiprid did not increase in pears with increasing post-treatment intervals (1, 4, 7 and 10 days following the last application).

The results from trials conducted in zones applicable to Canada carried out at the same application rate as those in unique U.S. zones have shown that the MRLs observed are lower in zones applicable to Canada for apples. In contrast, the residues observed in pears were higher in Canadian zones than the those observed in U.S. zones.

Based on the U.S. data alone for apples and pears, the proposed crop group tolerance of 0.7 ppm is appropriate. However, the maximum acetamiprid residues observed in pome fruit grown in Canada were 0.71 ppm (in pears). This result is in sharp contrast to the general trend observed for all crops in this petition. Generally, the residues of acetamiprid observed in Canada were much lower than those observed in the U.S. The available U.S. and Canadian data for apples and pears indicate that a tolerance level or MRL of 1.0 ppm would be appropriate.

Both the EPA and the PMRA have determined that the supervised crop field trials for pome fruits are acceptable. The number and location of the trials satisfy the U.S. guideline requirement for crop field trials however, the number and location of the trials submitted does not satisfy the requirements set out in DIR98-02. Due to the high quality of the data submitted, the PMRA has decided to grant the registrant partial relief from the full requirements of DIR98-02. Consequently, the PMRA will only require one additional trial for apples an zone 5B and one additional trial carried out in zone 1A on pears as a condition of the Canadian registration.

The results from the grape supervised crop field trials carried out in U.S. zones have shown that the MRL in grapes was 0.14 ppm. The MRL observed in trials carried out in zones applicable to Canada was 0.084 ppm.

The number and location of these trials satisfy the U.S. guideline requirement for crop field trials; however, the number and location of the trials submitted does not satisfy the requirements set out in the Canadian residue chemistry guidelines. Due to the high quality of the data submitted, the PMRA has decided to grant the registrant partial relief from the full requirements of DIR98-02. Consequently, the PMRA will only require two additional trial carried out in zone 5 as a condition of registration.

Based on the available U.S. and Canadian data, an MRL of 0.2 ppm would be adequate to cover residues of acetamiprid in or on grapes.

The results from the supervised crop field trials in cottonseed and cotton gin trash have shown that the MRLs in undelinted cottonseed and gin trash were 0.50 ppm for undelinted cottonseed and 19.2 ppm for cotton gin trash.

The EPA has determined that the supervised crop field trials for cotton are acceptable and that the trials location and number satisfy the guideline requirement.

Based on the available data for cotton, The U.S. will set tolerances of 0.6 ppm for cottonseed and 20 ppm for cotton gin trash. There are currently no Codex MRLs established for acetamiprid; Mexican MRLs have been established for cottonseed at 0.010 ppm and potato at 0.5 ppm. Upon further investigation, the difference between the tolerance recommended by the EPA and the allowable levels in Mexico are related to the formulation and the timing of application. **Canada will recommend an MRL of 0.6 ppm to cover potential residues of acetamiprid in cottonseed.** This MRL will harmonize with the U.S. and will also allow for the import of Mexican cottonseed products.

Residue decline studies with acetamiprid have been conducted with representative crops including cotton, head lettuce, oranges, pears and pepper. These studies indicate that generally, residues of acetamiprid did not increase with increasing post-treatment intervals following the last application. Therefore, no decline study with apples will be required.

Processing studies were carried out in tomato, oranges, apple, grape and cotton.

In tomato, concentration factors of 1.4× and 3.0× for tomato puree and paste, were determined. The highest average field trial (HAFT) residue from tomato trials reflecting the maximum proposed use pattern is 0.10 ppm. Based on the HAFT and the concentration factors, the maximum expected acetamiprid residues in tomato puree and paste would be 0.14 ppm and 0.3 ppm, respectively. The expected residues in tomato puree are less than the proposed MRL for tomato raw agricultural commodity (RAC) (0.2 ppm); therefore, a separate MRL does not need to be established for tomato puree. However, an MRL needs to be established to cover residues of acetamiprid in tomato paste. **An MRL of 0.4 ppm for residues of acetamiprid in tomato paste is recommended**.

In oranges, concentration factors of <0.16×, 2.8× and <0.16× for juice, dried pulp and citrus oil, respectively, were experimentally derived. The HAFT residue from citrus trials reflecting the maximum proposed use pattern is 0.34 ppm (in lemons). Based on the HAFT and the concentration factors, the maximum expected acetamiprid residues in juice, dried pulp and oil would be <0.06 ppm, 1.0 ppm and <0.06 ppm, respectively. The expected residues in juice and citrus oil are less than the proposed MRLs for citrus RAC (0.5 ppm); therefore, MRLs do not need to be established for citrus juice or oil. However, an MRL needs to be established to cover residues of acetamiprid in citrus dried pulp. **A tolerance or MRL of 1.2 ppm for residues of acetamiprid in citrus dry pulp is proposed.**

In apples, the registrant has submitted data that illustrated that residues of acetamiprid has concentration factors of 0.88× and 1.4× for apple juice and wet apple pomace, respectively. The HAFT residue from apple trials reflecting the maximum proposed use pattern is 0.59 ppm. Based on the HAFT and the concentration factor, the maximum expected acetamiprid residues in wet apple pomace would be 0.83 ppm, respectively. **Because residues did not concentrate in apple juice, no MRL for acetamiprid residues in apple juice is required.**

In grapes, the maximum theoretical concentration factors are 1.2× for grape juice and 4.7× for raisins. Since the observed factor for juice exceeds the maximum theoretical factor, the theoretical factor will be used to calculate the expected residues in grape juice. The HAFT residue from grape trials reflecting the maximum proposed use pattern is 0.13 ppm. Based on the HAFT and the concentration factors (experimental for raisins and theoretical for juice), the maximum expected acetamiprid residues in grape juice and raisins would be 0.16 and 0.12 ppm, respectively. **The expected residues in grape juice and raisins are less than the proposed MRL for grape RAC (0.2 ppm); therefore, MRLs do not need to be established for grape juice and raisins.**

In the processed food study on cotton, the registrant was able to determine average concentration or reduction factors of 0.38×, 0.80× and <0.04× for meal, hulls and refined oil, respectively. **Because residues of acetamiprid did not concentrate in cottonseed processed commodities, no MRLs for cotton refined oil need to be established.**

Meat, milk, poultry, eggs

Acetamiprid was administered orally to nine **Holstein dairy cows** for 28 days. The dosages were equivalent to 6 ppm (1.3×), 18 ppm (4.0×) and 60 ppm (13×) in the diet. Potential ruminant feed items associated with this petition are wet apple pomace, canola meal, dried citrus pulp, undelinted cottonseed, cotton gin byproducts, cottonseed meal and hulls. Based on the supervised field trials, cotton gin byproducts would be expected to contribute the highest acetamiprid residues to cattle dietary burden. Using a diet consisting of cotton gin byproducts and cottonseed meal, the maximum theoretical dietary burden of acetamiprid to dairy cattle is 4.545 ppm. These feed RACs represent 35% of the total diet for dairy and beef cattle; a diet consisting of other ruminant feed items associated with this petition, in addition to cotton gin byproducts and cottonseed meal, is not considered to be realistic. As cotton feed items are predominantly a U.S. feed item the anticipated dietary burden to cattle in Canada is considerably less. The expected residues of acetamiprid in milk, meat, and meat byproducts resulting from the feeding of crops treated with acetamiprid under the conditions proposed in this petition are <0.01–0.018 ppm in milk, <0.01 ppm in fat and muscle, and <0.05 ppm in kidney and liver. The metabolism studies indicated that the residues of concern in ruminant commodities are the combined residues of acetamiprid and IM-2-1. **MRLs of 0.1 ppm for meat, fat and milk and 0.3 ppm for meat byproducts are recommended.**

The lactating goat metabolism study also indicated that IM-2-1 serves as a marker compound for IM-2-1-amide. Based on data from the lactating goat metabolism study, IM-2-1-amide occurs at not more than 10 times the level of IM-2-1 in ruminant muscle tissues. Though IM-2-1 is not included in the ROC for monitoring purposes, it presence must be accounted for in the dietary risk assessment (DRA).

In the **poultry feeding** study acetamiprid was administered orally to 30 White Leghorn laying hens for 28 days. The dosages were equivalent to 1.2 ppm (9.8×), 3.6 ppm (30×) and 12 ppm (98×) in the diet. Potential poultry feed items associated with this petition are canola meal and cottonseed meal. Using a diet consisting of canola meal and cottonseed meal, the maximum theoretical dietary burden (MTDB) of acetamiprid to poultry is 0.122 ppm. These feed RACs represent 35% of the total diet for poultry. As cotton feed items are primarily of U.S. origin, the calculated MTDB is an overestimate for Canadian poultry. The expected residues of acetamiprid in eggs, meat and meat byproducts resulting from the feeding of crops treated with acetamiprid under the conditions proposed in this petition are <0.01 ppm in eggs, fat and muscle, and <0.05 ppm in liver. Expected residues of the metabolite IM-2-1 are 0.01 ppm in liver, 0.003 ppm in eggs, and <0.01 ppm in fat and muscle. The residues of concern in livestock and poultry are acetamiprid and IM-2-1. **MRLs at the LOQ for poultry commodities (0.01 ppm for muscle, fat and eggs; 0.05 ppm for organ meats and meat byproducts) will be proposed**.

The **confined crop rotation** studies indicated that no field rotational crop studies are needed at this time.

All of the dietary risk analysis was carried out using the Dietary Exposure Evaluation Model™ (DEEM™) Software. The assessment was conducted using the 1994–1998 Continuing Survey of Food Intake for Individuals.

It was estimated that the chronic dietary exposure to acetamiprid from food and water represented approximately 78.4% of the ADI for the highest exposed subpopulation, which was children 1–6 when MRL values are used in the calculation. The potential daily intake (PDI) for the remaining population subgroups, including infants, children, adults and seniors, each represented <78.4% of the ADI.

A more refined dietary risk assessment of the chronic exposure resulting from food and water indicated that approximately 27.7% of the ADI for the highest exposed subpopulation, which was children 1–6 when refined values are used in the calculation. The PDI for the remaining population subgroups, including infants, children, adults and seniors, each represented <28% of the ADI.

It was estimated that the acute dietary exposure (95th percentile deterministic) to acetamiprid from food and water represented approximately 50.1% of the ARfD for children 1–6. The PDI for the remaining population subgroups, including infants, children, adults and seniors, each represented <50.1% of the ARfD.

The carcinogenic potential of acetamiprid was assessed by PMRA, which concluded that acetamiprid as not likely to be carcinogenic to humans. A cancer risk assessment is not required for this chemical.

Consequently, the consumption estimates coupled with the MRLs indicated that there is adequate protection of the consumer, including infants, children, adults and seniors, from dietary residues of acetamiprid following use in accordance with Good Agricultural Practices (GAP).

5.0 Fate and behaviour in the environment

See Appendix V for summary tables.

5.1 Physical and chemical properties relevant to the environment

Acetamiprid was determined to be very soluble in water, which indicates high potential for the compound to leach in soil or to runoff in surface water. The vapour pressure of acetamiprid at 25°C indicates that the compound would be considered relatively non-volatile under field conditions. The Henry's Law Constant of acetamiprid indicates that the chemical will not be volatile from water and moist soil surfaces. The magnitude of K_{ow} for acetamiprid indicates that there is no potential for bioaccumulation. The pK_a of the compound indicated a potential for mobility in soil. The UV/visible absorption spectrum of acetamiprid indicates that the compound is not likely to phototransform at environmentally relevant wavelengths of light.

5.2 Abiotic transformation

Acetamiprid was stable to hydrolysis in pH 4, 5 and 7 solutions at all temperatures and in pH 9 at 22°C, but hydrolysed at high temperatures (35 and 45°C) in pH 9 solution. Two major hydrolytic transformation products, IM-1-3 and IM-1-4, were formed in the pH 9 solution. These results indicated that acetamiprid was stable to hydrolysis over a wide range of pH values and environmentally relevant temperatures. The rate of phototransformation of acetamiprid on soil was less than the rate of transformation in dark controls and the study was deemed to be scientifically invalid. The results of phototransformation study in aqueous solution at pH 7 yielded a half life of 34 days. One major phototransformation product, UK1 (also referred to as IB-1-1), was formed in water. IM-1-4, a major hydrolytic transformation product of acetamiprid, slightly phototransformed in aqueous solution. Abiotic transformation, therefore, will not be an important route of transformation of acetamiprid in the environment.

5.3 Biotic transformation

Results of biotransformation studies with acetamiprid in three soils from the UK (loam, sandy loam, and clay loam) and one soil from Switzerland (loamy sand) under aerobic conditions at 20°C yielded half life values of ~1–8 days, with the formation of several

major transformation products: IM-1-4, IM-1-5 and IC-0. Under aerobic conditions at 10°C, the half life of acetamiprid in a loam soil from the UK was determined to be ~7 days, with the formation of one major transformation product, IM-1-4. While the biotransformation of the major transformation products IM-1-4 and IM-1-5 was not investigated, the half-life of IC-0 in the three soils from UK under aerobic conditions at 20°C ranged from 3.5 to 6.5 days, with the formation of several minor transformation products. These results indicate that acetamiprid will be non-persistent in the soil according to the classification system of Goring et al. (1975). Biotransformation of acetamiprid in soil under anaerobic conditions was not investigated. However, based on the results of anaerobic aquatic biotransformation study, acetamiprid will be persistent under anaerobic conditions.

Results of biotransformation studies in an aerobic sediment–water system at 25°C yielded a half-life value of 30 days, with the formation of three major transformation products: IM-1-4, IC-0 and IM-1-2. The half-life of acetamiprid in an anaerobic water/sediment system at 25°C was 365 days, with the formation of one major transformation product: IM-1-4. These results indicate that acetamiprid will be slightly persistent in aerobic and persistent in anaerobic aquatic systems according to the classification scheme of McEwen and Stephenson (1979).

Biotransformation will be an important route of dissipation of acetamiprid under aerobic conditions in the environment.

5.4 Mobility

The adsorption K_d and K_{oc} values for acetamiprid in four soils (loamy sand I, loamy sand II, silt loam and clay) and one pond sediment (sandy loam) ranged from 0.34 to 4.1 mL/g and from 157 to 298 mL/g, respectively. The adsorption K_d and K_{oc} values for the transformation product IM-1-4 in the four soils and the sediment ranged from 0.38 to 22 mL/g and 153 to 1841 mL/g, respectively. The adsorption K_d and K_{oc} values for the transformation product IC-0 in the four soils and the pond sediment ranged from <1 to 2.4 mL/g and 34 to 177 mL/g, respectively. These results indicate that acetamiprid, based on K_{oc} values, will be of moderate mobility in soil and has a moderate potential to partition into sediment. Based on the adsorption K_{oc} values, IM-1-4 will be of low to moderate mobility and IC-0 will be of very high to moderate mobility in the soil. Based on the values for vapour pressure and Henry's Law Constant, volatilization of acetamiprid is not expected to be a route of dissipation.

5.5 Dissipation and accumulation under field conditions

Results of terrestrial field studies of dissipation and accumulation conducted in Canada indicated that acetamiprid was non-persistent to slightly persistent in soil, with time required for non first-order 50% dissipation (DT_{50}) values ranging from 5.2 to 17.8 days. No significant carryover of residues to the next field season is expected to occur based on these results. The major transformation products of acetamiprid, IM-1-4, IC-0 and

IM-1-2, showed a trend of declining concentrations in soil towards the end of the study at all sites except in Manitoba, where concentrations of IM-1-4 increased and IC-0 was detected once at the end of the study. There was no evidence of leaching of acetamiprid or its major transformation products though the soil layers. However, field conditions were not favourable for leaching owing to insufficient rainfall. Due to the moderately rapid rate of degradation of the parent in soil, however, it is unlikely that leaching would present a significant route of dissipation for the parent compound. Field dissipation studies conducted in the U.S. (Washington, Florida, New York, California and New Jersey) yielded DT_{50} values ranging from 2.8 to 14.1 days. Acetamiprid and its major transformation products were not detected below the top (0–15 cm) layer of soil, with the exception of a single detection of IC-0 at the California site. The Canadian and U.S. studies, however, are classified as supplementary owing to deficiencies.

5.6 Bioaccumulation

A study of bioaccumulation of acetamiprid in fish was not submitted. Given the magnitude of K_{ow}, however, acetamiprid is not expected to bioaccumulate in organisms.

5.7 Summary of fate and behaviour in the terrestrial environment

Acetamiprid was determined to be very soluble in water, which indicates high potential for the compound to leach in soil or to runoff in surface water. The vapour pressure of acetamiprid at 25°C indicates that the compound would be considered relatively non-volatile under field conditions. The Henry's Law Constant of acetamiprid indicates that the chemical will not be volatile from water and moist soil surfaces. The magnitude of K_{ow} for acetamiprid indicates that there is no potential for bioaccumulation. The pK_a of the compound indicates a potential for mobility in soil. The UV/visible absorption spectrum of acetamiprid indicates that the compound is not likely to phototransform at environmentally relevant wavelengths of light.

Acetamiprid was stable to hydrolysis in pH 4, 5 and 7 solutions at all temperatures and in pH 9 at 22°C, but hydrolysed at high temperatures (35 and 45°C) in pH 9 solution. Two major hydrolytic transformation products, IM-1-3 and IM-1-4, were formed at pH 9. These results indicated that acetamiprid was stable to hydrolysis over a wide range of pH values and at environmentally relevant temperatures. The rate of phototransformation of acetamiprid on soil was less than the rate of transformation in dark controls and the study was deemed to be scientifically invalid. Abiotic transformation will not be an important route of transformation of acetamiprid in the environment.

Results of biotransformation studies with acetamiprid in three soils from the UK (loam, sandy loam, and clay loam) and one soil from Switzerland (loamy sand) under aerobic conditions at 20°C yielded half life values of ~1–8 days, with the formation of several major transformation products: IM-1-4, IM-1-5 and IC-0. Under aerobic conditions at 10°C, the half life of acetamiprid in a loam soil from the UK was determined to be ~7 days, with the formation of one major transformation product, IM-1-4. While the

biotransformation of the major transformation products IM-1-4 and IM-1-5 was not investigated, the half-life of IC-0 in the three soils from UK under aerobic conditions at 20°C ranged from 3.5 to 6.5 days, with the formation of several minor transformation products. These results indicate that acetamiprid will be non-persistent in the soil according to the classification system of Goring et al. (1975). Biotransformation of acetamiprid in soil under anaerobic conditions was not investigated. However, based on the results of anaerobic aquatic biotransformation study, acetamiprid will be persistent under anaerobic conditions.

The adsorption K_d and K_{oc} values for acetamiprid in four soils (loamy sand I, loamy sand II, silt loam and clay) and one pond sediment (sandy loam) ranged from 0.34 to 4.1 mL/g and from 157 to 298 mL/g, respectively. The adsorption K_d and K_{oc} values for the transformation product IM-1-4 in the four soils and the sediment ranged from 0.38 to 22 mL/g and 153 to 1841 mL/g, respectively. The adsorption K_d and K_{oc} values for the transformation product IC-0 in the four soils and the pond sediment ranged from <1 to 2.4 mL/g and 34 to 177 mL/g, respectively. These results indicate that acetamiprid, based on K_{oc} values, will be of moderate mobility in soil. Based on the adsorption K_{oc} values, IM-1-4 will be of low to moderate mobility and IC-0 will be of very high to moderate mobility in the soil. Based on the values for vapour pressure and Henry's Law Constant, volatilization of acetamiprid is not expected to be a route of dissipation.

Results of terrestrial field studies of dissipation and accumulation conducted in Canada indicated that acetamiprid was non-persistent to slightly persistent in soil, with DT_{50} values ranging from 5.2 to 17.8 days. No significant carryover of residues to the next field season is expected to occur based on these results. The major transformation products of acetamiprid, IM-1-4, IC-0 and IM-1-2, showed a trend of declining concentrations in soil towards the end of the study at all sites except in Manitoba, where concentrations of IM-1-4 increased and IC-0 was detected once at the end of the study. There was no evidence of leaching of acetamiprid or its major transformation products though the soil layers. Field dissipation studies conducted in the U.S. (Washington, Florida, New York, California and New Jersey) yielded DT_{50} values ranging from 2.8 to 14.1 days. Acetamiprid and its major transformation products were not detected below the top (0–15 cm) layer of soil, with the exception of a single detection of IC-0 at the California site. The Canadian and U.S. studies, however, are classified as supplementary owing to deficiencies.

5.8 Summary of fate and behaviour in the aquatic environment

Acetamiprid was stable to hydrolysis at pH 4, 5 and pH 7 solutions at all temperatures and in pH 9 at 22°C, but hydrolysed at high temperatures (35 and 45°C) in pH 9 solution. At all pHs and temperatures, two major hydrolytic transformation products, IM-1-3 and IM-1-4, were formed. These results indicated that acetamiprid was stable to hydrolysis at a wide range of pH values and environmentally relevant temperatures. Hydrolysis, therefore, will be not be a route of transformation of acetamiprid in the aquatic environment.

The results of phototransformation study with acetamiprid in aqueous solution at pH 7 yielded a half life of 34 days. One major phototransformation product, UK1 (also referred to as IB-1-1), was formed in water. IM-1-4, a major hydrolytic transformation product of acetamiprid, slightly phototransformed in aqueous solution. Phototransformation, therefore, may be a minor route of transformation in the photic zone of clear natural water.

Results of biotransformation studies in an aerobic sediment–water system at 25°C yielded a half-life value of 30 days, with the formation of three major transformation products: IM-1-4, IC-0 and IM-1-2. The half-life of acetamiprid in an anaerobic water/sediment system at 25°C was 325 days, with the formation of one major transformation product: IM-1-4. These results indicate that acetamiprid will be slightly persistent in aerobic and persistent in anaerobic sediment–water systems. Acetamiprid, based on K_{oc} values, has a moderate potential to partition into sediment.

A study of bioaccumulation of acetamiprid in fish was not submitted. Given the magnitude of K_{ow}, however, acetamiprid is not expected to bioaccumulate in organisms.

5.9 Expected environmental concentrations

In this review, the concentrations of acetamiprid in various environmental compartments were estimated based on calculations using maximum-exposure scenarios. It was assumed that, as per the label rates revised by the Efficacy and Sustainability Assessment Division for Assail Brand 70 WP, a maximum of four applications per growing season was made at the maximum rate of 168 g a.i./ha at an interval of 9 days.

5.9.1 Soil

Assuming a soil bulk density of 1.5 g/cm^3, a soil depth of 15 cm, and a scenario in which the product is applied to bare soil, the expected environmental concentration (EEC) of residues in soil would be 0.19 mg a.i./kg soil.

5.9.2 Aquatic systems

Assuming a water density of 1.0 g/mL, a water depth of 30 cm, and a scenario in which a body of water is over-sprayed with the product, the EEC in water would be 0.16 mg a.i./L water.

For drinking water, the Level I EECs for acetamiprid in groundwater, calculated using the model LEACHM, and in surface water, calculated using the model PRZM/EXAM, are reported in Appendix V, Table 3.

5.9.3 Vegetation and other food sources

The applicant did not submit data on the concentrations of acetamiprid on crops immediately after application. Therefore, residue concentrations on vegetation were estimated using a nomogram developed by the U.S. EPA from the data of Hoerger and Kenaga (1972), modified by Fletcher et al. (1994), for use in ecological risk assessment (Urban and Cook, 1986) (Appendix V, Table 4). A wet to dry weight conversion was also calculated.

6.0 Effects on non-target species

6.1 Effects on terrestrial organisms

The 14-day acute toxicity study with the earthworm, *Eisenia foetida*, was classified as unacceptable and does not satisfy the guideline requirements. The acute contact median lethal concentration (LC_{50}) and no observable effect concentration (NOEC) of acetamiprid to the honeybee, *Apis mellifera*, were 8.09 µg a.i./bee and 6.25 µg a.i./bee, respectively. The acute oral median lethal dose (LD_{50}) and no observable effect level (NOEL) of acetamiprid to *A. mellifera* were 14.5 µg a.i./bee and 1.38 µg a.i./bee, respectively. Acetamiprid, therefore, is classified as moderately toxic to the honeybee according to the criteria of Atkins et al. (1981).

The acute (14-d) oral LD_{50} and NOEL of acetamiprid to the mallard duck (*Anas platyrhynchos*) were 84 mg a.i./kg bw and <43 mg a.i./kg bw, respectively. The subacute (5-d) dietary toxicity study in *A. platyrhynchos* was classified as supplementary and does not satisfy the guideline requirement for a subacute dietary toxicity study for the mallard duck. The subacute (5-d) dietary toxicity study with the bobwhite quail (*Colinus virginianus*) was classified as supplementary owing to deficiencies in the study. The one-generation reproductive toxicity study in *C. virginianus* was classified as supplemental and does not satisfy the guideline requirement for a bobwhite quail reproduction study. The NOEC and lowest observable effect concentration (LOEC) of acetamiprid on the reproduction of *A. platyrhynchus*, however, were 250 mg a.i./kg diet and 500 mg a.i./kg diet, respectively. Based on the results of the toxicity studies, acetamiprid is classified as moderately toxic to the mallard duck on an acute basis in accordance with the classification system of the U.S. EPA.

The acute (5-d) dietary LC_{50} and NOEC of the transformation product IM-1-4 to *A. platyrhynchos* were >5000 mg a.i./kg diet and 500 mg a.i./kg diet, respectively. Based on the results of the toxicity studies, the transformation product IM-1-4 is classified as virtually non-toxic to the mallard duck on a dietary basis in accordance with the classification system of the U.S. EPA.

Acetamiprid was determined to be highly toxic to rats when administered as a single dose via the oral route (LD_{50} = 146 mg/kg bw). The clinical symptoms in dosed rats included crouching, tremors, low sensitivity, prone position, urinary incontinence and ataxia.

Acetamiprid was reported to be of low toxicity to rats when administered via the dermal route (LD_{50} > 2000 mg/kg bw). There were no clinical signs of toxicity in the test animals and no abnormal observations at necropsy. Acetamiprid was slightly toxic to rats when administered by the inhalation route (LC_{50} > 1.15 mg/L). Clinical symptoms included whole body tremors, brown staining around eyes, hair loss from the body, lethargy and discharge from snout. Acetamiprid was found to be non-irritating to the skin and minimally irritating to the eye of rabbits, and non-sensitizing to the skin of guinea pig.

Repeated short-term oral dosing of acetamiprid to Beagle dogs resulted in lower body weight gains, lower food consumption, significant loss of body weight and slight decline in kidney and liver weights (NOAEL = 16.7 mg/kg bw/d for males and 19.1 mg/kg bw/d for females). Oncogenicity studies with mice and rats indicated increased incidence of hepatocellular hypertrophy, hepatocellular vacuolation, decrease in body weights, decrease in body weight gain and changes in organ weights consistent with effect on body weight (NOAEL = 65.6 and 7.1 mg/kg bw/d, respectively). There was, however, no evidence of oncogenicity. Acetamiprid was not genotoxic and non-mutagenic in a standard battery of genotoxicity and mutagenicity tests such as bacterial reverse mutation (Ames test), mammalian gene mutation, and mammalian cytogenetics (micronucleus assay), but showed slight positive response in the Chinese hamster ovary cell study for chromosomal aberration in vitro. Acetamiprid was not neurotoxic to rats and non-teratogenic to rats and rabbits.

In a multi-generation reproduction study with rats (effects on pregnancy and fetuses), acetamiprid caused a decrease in body weight, body weight gain and food consumption, decrease in litter size, viability and weaning in F_2 pups, decrease in litter weights and individual pup weights and delayed eye opening and pinna unfolding (NOAEL = 17.9 mg/kg bw/d, for reproductive effects). Also, there was qualitative evidence of sensitivity of the offspring.

Studies on the effect of acetamiprid on the seedling emergence and vegetative vigour of monocot: corn (*Zea mays*), oat (*Avena sativa*), onion (*Allium cepa*) and perennial ryegrass (*Lolium perenne*), and dicot: cabbage (*Brassica oleracea*), cucumber (*Cucumis sativus*), lettuce (*Lactuca sativa*), soybean (*Glycine max*), tomato (*Lycopersicon esculentum*) and turnip (*Brassica rapa*) crops indicated that, for seedling emergence, the most sensitive monocot species was onion, with a concentration effective against 25% of test organisms (EC_{25}) of 257.8 g a.i./ha, and the most sensitive dicot species was cucumber, with an EC_{25} of 179.3 g a.i./ha. For vegetative vigour, the most sensitive monocot species was perennial ryegrass, with an EC_{25} of 515.6 g a.i./ha, and the most sensitive dicot species was lettuce, with an EC_{25} of 17.9 g a.i./ha.

6.2 Effects on aquatic organisms

Freshwater

The study of acute (48-h) median effective concentration (EC_{50}) of acetamiprid to the water flea (*Daphnia magna*) was determined to be deficient and does not fulfill the U.S.

EPA's guideline requirements. The chronic (21-d) EC_{50} of acetamiprid to the same species was 86 mg a.i./L. The corresponding NOEC for *D. magna* was 5 mg a.i./L. The acute (48-h) EC_{50} of the transformation products IM-1-4, IM-1-2 and IC-0 to *D. magna* were 43.9, >99.8 and >95.1 mg/L, respectively. The respective NOECs for *D. magna* were 6.9 mg/L, 99.8 mg/L and 95.1 mg/L. Based on the results of these studies, the transformation products IM-1-4, IM-1-2 and IC-0 are classified as slightly toxic to daphnids in accordance with the classification system of the U.S. EPA.

The acute (96-h) LC_{50} of acetamiprid to the rainbow trout (*Oncorhynchus mykiss*) and the bluegill sunfish (*Lepomis macrochirus*) were >100 and >119.3 mg a.i./L, respectively. The corresponding NOEC of acetamiprid to these species was 35 and <11.8 mg a.i./L, respectively. The chronic (35-d) LC_{50} and NOEC of acetamiprid to the early life-stages of the fathead minnow (*Pimephales promelas* were 95.8 and 19.2 mg a.i./L, respectively. The acute (96-h) LC_{50} and LOEC of the transformation product IM-1-4 to *O. mykiss* were >98.1 and 8.6 mg/L, respectively. Based on the results of the acute toxicity studies, acetamiprid is classified as practically nontoxic to the rainbow trout and the bluegill sunfish and IM-1-4 is slightly toxic to the rainbow trout, in accordance with the classification system of the U.S. EPA.

The acute EC_{50} of acetamiprid to the algae, *Selenastrum capricornutum* and *Anabaena flos-aquae*, and the diatom, *Navicula pelliculosa*, were >1.2 mg a.i./L, >1.3 mg a.i./L and >1.1 mg a.i./L, respectively. The respective NOECs for the three species were 1.2 mg a.i./L, 1.3 mg a.i./L and 1.1 mg a.i./L. The acute (14-d) EC_{50} and NOEC of acetamiprid to the duckweed (*Lemna gibba*) were >1.0 mg a.i./L and 1.0 mg a.i./L, respectively.

Marine or estuarine

The acute (96-h) LC_{50} of acetamiprid to the saltwater mysid (*Mysidopsis bahia*) and the acute (96-h) EC_{50} (for shell deposition) to the Eastern oyster (*Crassostrea virginica*) were 66 µg a.i./L and 41 mg a.i./L, respectively. The respective NOECs for the two species were 13 µg a.i./L and <14 mg a.i./L. The chronic (28-d) NOEC to *M. bahia* was 2.5 µg a.i./L. The acute (96-h) LC_{50} of the transformation product IM-1-4 to *M. bahia* was 19 mg/L. Based on the results of the toxicity studies, acetamiprid is classified as very highly toxic to *M. bahia* and slightly toxic to *C. virginica* on an acute basis in accordance with the classification system of the U.S. EPA. The transformation product IM-1-4 is classified as slightly toxic to *M. bahia* using the same classification system.

The acute (96-h) LC_{50} and NOEC of acetamiprid to the sheepshead minnow (*Cyprinodon variegatus*) were 100 mg a.i./L and 55 mg a.i./L, respectively. Based on the results of the acute toxicity test, acetamiprid is classified as slightly toxic to *C. variegatus* in accordance with the classification system of the U.S. EPA.

The acute EC_{50} and NOEC of acetamiprid to a marine diatom (*Skeletonema costatum)* were >1.0 mg a.i./L and 1.0 mg a.i./L, respectively.

6.3 Effects on biological methods of sewage treatment

Not applicable for the proposed use.

6.4 Risk characterization

6.4.1 Environmental behaviour

Acetamiprid is slightly persistent under aerobic aquatic conditions, but persistent under anaerobic aquatic conditions. Acetamiprid is non-persistent to slightly persistent in soil and, therefore, no significant carryover of residues to the next field season is expected. Acetamiprid is not likely to leach through soil layers. However, acetamiprid has a potential for partitioning into the aquatic sediment. The principal routes of transformation are biotransformation in soil and in aquatic environments. It is not expected to volatilize from water and moist soils. The persistence and mobility of the major transformation products IM-1-5 and IB-1-1 (UK-1) are unknown.

6.4.2 Terrestrial organisms

The risk to non-target organisms was calculated using EEC values of 0.19 mg a.i./kg in a 15-cm depth of soil and 0.16 mg a.i./L in a 30-cm depth of water. The EEC in wildlife food sources, expressed in mg a.i./kg dw, are shown in Appendix V, Table 4. Margins of safety were calculated using the NOEC or an estimated NOEC equivalent to 1/10 of the EC_{50} or LC_{50}, and EC_{25} for terrestrial plants, for the most sensitive species per group.

Non-target terrestrial invertebrates
The 14-day acute toxicity study with the earthworm (*Eisenia foetida*) was classified as unacceptable and does not satisfy the guideline requirements. Therefore, the risk posed by acetamiprid to earthworms cannot be assessed.

The acute contact NOEC of acetamiprid to the honeybee (*Apis mellifera*) is 6.25 µg a.i./bee. Acetamiprid is classified as moderately toxic to honeybees according to the classification scheme of Atkins (1981). The compound will, therefore, pose a hazard to honeybees exposed to direct application.

Terrestrial plants
The results of a multi-dose phytotoxicity study conducted with acetamiprid indicated that the EC_{25} for the most sensitive end point for vegetative vigour, plant weight in lettuce, was 17.9 g a.i./ha and the EC_{25} for the most sensitive end point for seedling emergence, shoot length in cucumber, was 179.3 g a.i./ha.

These results indicate that acetamiprid will pose a moderate risk (margin of safety (MOS) = 0.1) to the vegetative vigour, but a low risk (MOS = 1.06) to seedling emergence, in non-target vegetation if exposure of the non-target vegetation occurs by overspray.

Wild birds

The most sensitive end point is adverse effects on reproduction of the mallard duck (*Anas platyrhynchos*), with a NOEC of 250 mg a.i./kg diet. The reproduction study with bobwhite quail (*Colinus virginianus*) was classified as unacceptable and does not satisfy the guideline requirements. Therefore, the risk posed by acetamiprid to bobwhite quail reproduction cannot be assessed.

Wild birds, such as mallard duck, could be exposed to acetamiprid residues as a result of spray drift or consumption of sprayed vegetation or contaminated prey. The mallard duck diet may consist of approximately 10% large insects or snails, 10% leafy plants and 80% grain (EPA, 1993). Since the EECs of acetamiprid on large insects, leaves/leafy plants and grain are 14.48, 527.78 and 14.48 mg a.i./kg dry weight, respectively (Appendix V, Table 4), the estimated ingestion of acetamiprid through contaminated food sources by the mallard can be calculated as follows:

$$(0.10 \times 14.48) + (0.10 \times 527.78) + (0.80 \times 14.48) = 65.81 \text{ mg a.i./kg dw}$$

The mallard duck (live weight 1.2 kg) daily consumes food equivalent to 4.17% of its body weight (Urban and Cook, 1986). Therefore, the bird would acquire a dose of:

$$(0.041 \times 1200) \times 65.81 \div 1000 = 3.23 \text{ mg a.i./d}$$
$$\text{equivalent to: } (1000 \div 1200) \times 3.23 = \mathbf{2.7} \text{ mg a.i./kg bw/d}$$

This value is lower than the NOEC for the mallard duck (converted to 10.42 mg a.i./kg bw/d) at which there were no adverse reproductive effects on the test birds. It is, therefore, expected that acetamiprid will not pose a risk to the mallard duck (MOS = 3.86) on a reproductive effects basis.

Wild mammals

The most likely route for exposure of wild mammals to acetamiprid would be through consumption of contaminated prey or vegetation following operational applications of acetamiprid insecticide. Assuming an MRL of 302.54 mg a.i./kg in short range grass (dry weight basis), and 84.65 mg a.i./kg in small insects (dry weight basis), dosage levels immediately following application resulting from several maximum-exposure scenarios can be estimated. For example, the eastern cottontail rabbit, *Sylvilagus floridanus* (live weight: 1.3 kg), consuming short grass at a rate of 4.4% of its body weight per day (Dalke and Sime, 1941; Banfield, 1974), would consume 57.2 g of food per day and acquire a dose of 13.31 mg a.i./kg bw/d. The masked shrew, *Sorex cinereus* (live weight: 4 g), ingesting 25–75% of its body weight per day of contaminated small insects (Banfield, 1974) would consume 1–3 g of food per day and acquire a dose of 21.16–63.48 mg a.i./kg bw/d. The meadow vole, *Microtus pennsylvanicus* (live weight: 3.5 g), ingesting 15–24% of its body weight per day in grasses (Peterson, 1966) would consume 0.52–0.84 g of food/d and acquire a dose of 44.92–72.61 mg a.i./kg bw/d.

These estimated exposure dosages are less than the LD_{50}s from any of the acute toxicity studies, but exceed the NOELs from some of the subchronic/chronic studies. The results from some of these latter studies, however, likely overstate the effects that may occur in the field. The proposed use of acetamiprid insecticide in the field will result in limited exposure of wild mammals to the product and, therefore, is not expected to pose an appreciable risk to wild mammals.

6.4.3 Aquatic organisms

Non-target freshwater invertebrates
The most sensitive end point is chronic effects on the water flea, *Daphnia magna*, with an NOEC of 5 mg a.i./L. Given that the EEC of acetamiprid in water will be 0.16 mg a.i./L, acetamiprid will not pose a risk (MOS = 31.2) to aquatic invertebrates, such as the water flea.

Non-target marine or estuarine invertebrates
The most sensitive end point is chronic effects on the saltwater mysid, *Mysidopsis bahia*, with a NOEC of 2.5 µg a.i./L. Given that the EEC of acetamiprid in water will be 160 µg a.i./L, acetamiprid will pose a high risk (MOS = 0.015) to marine or estuarine invertebrates, such as the saltwater mysid in the absence of mitigation.

Fish
The most sensitive end point is acute effects on the bluegill sunfish, *Lepomis macrochirus*, with a NOEC of 11.8 mg a.i./L. Given that the EEC of acetamiprid in water will be 0.16 mg a.i./L, acetamiprid will not pose a risk (MOS = 73.7) to fish.

Aquatic plants and algae
The most sensitive end point is adverse effects on the freshwater diatom, *Navicula pelliculosa*, with an acute NOEC of 1.1 mg a.i./L. Given that the EEC of acetamiprid in water will be 0.16 mg a.i./L, acetamiprid will not pose a risk (MOS = 6.8) to aquatic organisms, such as the freshwater diatom.

6.5 Risk mitigation

Acetamiprid is slightly persistent under aerobic aquatic conditions but persistent under anaerobic aquatic conditions. Acetamiprid is non-persistent to slightly persistent in soil and, therefore, no significant carryover of residues to the next field season is expected. Acetamiprid is not likely to leach through soil layers. However, acetamiprid has a potential for partitioning into the sediment. The principal routes of transformation are biotransformation in soil and in aquatic environments. It is not expected to volatilize from water and moist soils. The persistence and mobility of the major transformation product IM-1-5 is unknown.

Acetamiprid will pose a high risk to marine or estuarine invertebrates, such as the mysid shrimp, and a moderate risk to terrestrial plants. Acetamiprid is toxic to honeybees exposed to direct treatment.

The risk to marine or estuarine organisms and terrestrial plants can be mitigated by the establishment of terrestrial and aquatic buffer zones. The risk to honeybees can be mitigated by precautionary label statement contraindicating application when bees present in the area to be treated.

Mitigative measures

Do not apply directly to water. Do not contaminate water used for irrigation or domestic purposes. Do not contaminate aquatic habitats, such as sloughs, coulees, ponds, prairie potholes, lakes, rivers, streams, reservoirs and wetlands, or terrestrial habitats, such as forested areas, shleter belts, woodlots, hedgerows, pastures, rangelands, and shrublands, when cleaning and rinsing spray equipment or containers. Overspray or drift to these sensitive habitats should be avoided.

A buffer zone of **20 m** for application by ground boom sprayer, and a buffer zone of **30 m** for application by air-blast/vineyard sprayer, is required between the downwind point of direct application and the closest edge of sensitive quatic habitats including sloughs, coulees, ponds, prairie potholes, lakes, rivers, streams, reservoirs and wetlands.

A buffer zone of **2 m** for application bo ground boom sprayer, and a buffer zone of **10 m** for application by air-blast/vineyard sprayer, is required between the downwind point of direct application and the closest edge of sensitive terrestrial habitats including forested areas, shelter belts, woodlots, hedgerows, pastures, rangelands and shrublands.

For ground application, do not apply during periods of dead calm or when winds are gusty.

For air-blast/vineyard sprayer, do not direct spray above trees/vines and turn off outward pointing nozzles at row ends and out rows. Do not apply during periods of dead calm, when winds re gusty or when wind speed is greater than 16 km/hr at the application site ad measured outside of the orchard/vineyard on the upwind site.

Acetamiprid is toxic to honey bees exposed to direct treatment. Do not pply when bees are present in the area to be treated.

7.0 Efficacy

7.1 Effectiveness

7.1.1 Intended uses

Aventis CropScience Canada Co. has applied for registration of two commercial class and one domestic class end-use products containing a new active ingredient, acetamiprid. The commercial class products contain 70% by weight of acetamiprid, while the domestic end-use product is a different formulation, containing 0.006% by weight of the active ingredient. The intended uses for the three products are summarized below.

Assail Brand 70 WP Insecticide (Commercial class): This product is for control of insect pests on agricultural food crops. The proposed USC for this product is USC 14, terrestrial food crops. The proposed label claims as well as application rates are listed as follows:

Proposed uses and application rate: Assail Brand 70 WP Insecticide						
Crop site	Pests	Rate (g/ha)		Seasonal maximum per crop site		
		Product	a.i.	No. of applications	Product (g/ha)	a.i. (g/ha)
Leafy vegetables	Aphids	56–120	39–84	5	600	420
Cole crops	Aphids Whitefly	56–120 120	39–84 84	5	600	420
Tomato	Aphids Colorado potato beetle Whitefly	56–120 40–120 120	39–84 28–84 84	4	480	336
Pome fruits	Aphids Tentiform leafminer Leafhoppers Codling moth Psylla	120–160 120–160 120–160 120–240 67–240	84–112 84–112 84–112 84–168 47–168	4	960	672
Grapes	Leafhoppers	80	56	2	160	112

Chipco Brand Tristar 70 WSP Insecticide (Commercial class): This product is for control of insect pests on greenhouse and outdoor non-food ornamental plants. The proposed USCs for this product are USC 6, greenhouse non-food crops, and USC 27, ornamentals outdoor. The proposed label claims as well as application rate are listed as follows:

Proposed uses and application rate: Chipco Brand Tristar 70 WSP Insecticide						
Crop site	**Pests**	**Rate (per 1000 L spray volume)**		**Seasonal maximum per crop site**		
		Product (packs)[a]	**a.i. (g)**	**No. of applications**	**Product (packs/ha)**	**a.i. (g/ha)**
Lathhouse, shadehouse, greenhouse and outdoor non-food flowering and ornamental plants	Aphids Whitefly European pine sawfly Leafhoppers Tentiform leafminer	3–10 5–10 5–10 5–10 8–15	34–112 56–112 56–112 56–112 90–168	2 (greenhouse, shadehouse, lathhouse) or 5 (outdoor)	55	616

[a] One pack contains 16 g of the product

Pristine Brand RTU Insecticide (Domestic class): This is a RTU product (no dilution is required) for control of insect pests on terrestrial food crops as well as outdoor ornamentals. The proposed USCs for this product are USC 14, terrestrial food crops and USC 27, ornamentals outdoor. The proposed label claims are listed as follows:

Proposed uses and application rate: Prisinte Brand RTU Insecticide		
Crops	Pests	Maximum no. of applications per season per crop site
Leafy vegetables	Aphids	5
Cole crops	Aphids, whiteflies	5
Tomato	Aphids, Colorado potato beetle, whiteflies	5
Pome fruits	Aphids, leafhoppers, tentiform leafminer	5
Outdoor flowers, ornamental plants	Aphids, European pine sawfly, leafhoppers, tentiform leafminer	5

7.1.2 Mode of action

Acetamiprid is a broad spectrum insecticide that belongs to a new class of compounds, the neonicotinoids. Neonicotinoids are believed to interfere with the nicotinic acetylcholine receptors of the insect's nervous system, although different compounds may have specific binding site(s) or receptor(s). Acetamiprid has a different mode of action than organophosphate, carbamate and pyrethroid insecticides. Acetamiprid is reported to

display translaminar and systemic activity and act through contact and ingestion although its hydrophobicity (penetration through insect cuticle) is considered to be low.

7.1.3 Crops

See Section 7.1.1.

7.1.4 Effectiveness against pests

USC 14: terrestrial food crops

Aphids (on field tomato, cole crops and leafy vegetables)
Twenty-six small-scale and operational-scale field trials were conducted in several U.S. states and two Canadian provinces (Ontario, Quebec) to determine the effectiveness of several rates of acetamiprid (39, 44, 49, 56, 84 g a.i./ha) in controlling aphids in fruiting vegetables (e.g., tomatoes), leafy vegetables (lettuce, spinach) and cole crops (broccoli, cabbage, cauliflower, collard, turnip). Aphid species tested included cabbage aphid, green peach aphid, lettuce seed stem aphid, turnip aphid, potato aphid and unspecified aphid species.

Adequate efficacy data were submitted to allow for the assessment of the efficacy of two proposed acetamiprid formulations (70 WP and 0.006% RTU) in controlling aphid pests in tomato and leafy and cole vegetable crops. Results from the trials showed that Assail Brand 70 WP Insecticide and Pristine Brand RTU Insecticide were effective in controlling aphid on tomato, cole and leafy vegetable crops. The 56 g a.i./ha rate is not significantly different from the high rate of 84 g a.i./ha in controlling aphid pests. No data were provided to justify the need for rates higher than 56 g a.i./ha.

Although applications at 56 g a.i./ha appeared to be consistently better than lower rates of 39–49 g a.i./ha, the data were not adequate to determine the lowest effective rate of product needed for control of aphid pests.

To conclude, the proposed use claim for control of aphids on field tomato and cole and leafy vegetable crops is acceptable at the rate of 39–60 g a.i. (56–86 g product)/ha (rounded from 56 g a.i./ha) for Assail Brand 70 WP Insecticide. Additional data are required for Assail Brand 70 WP Insecticide to establish the lowest effective rate for this use. The same proposed use claim is fully supported for Pristine Brand RTU Insecticide (a domestic, RTU product) based on the efficacy data of Assail and Pristine formulations.

Whitefly (on field tomato and cole crops)
Seven field trials and four small plot or greenhouse trials were conducted, respectively in several U.S. states, to assess efficacy of two proposed acetamiprid formulations (Assail Brand 70 WP Insecticide and Pristine Brand RTU Insecticide) in controlling whitefly in fruiting vegetables (e.g., tomatoes) and cole crops (broccoli, cabbage, collards). No trial was conducted on leafy vegetable crops.

For the formulation of Assail Brand 70 WP Insecticide, application of acetamiprid at 84 g a.i./ha consistently provided better control than rates of 44–49 g a.i./ha. The performance of acetamiprid at this rate were comparable to some commercial standards (esfenvalerate, permethrin and imidacloprid) and better than chlorpyrifos. Although a rate of 56 g a.i./ha provided good control of both whitefly nymphs and adults in one study, this is insufficient to establish 56 g a.i./ha as the lowest effective rate.

For the RTU formulation of Pristine Brand RTU Insecticide, the trial results showed that the acetamiprid 0.006% RTU provided very good control of adult (>90%) and nymphs (70–80%) of whitefly on broccoli and tomatoes. The results were similar to imidacloprid and diazinon RTU products.

To conclude, the proposed use claim for whitefly control on tomato and cole crops is acceptable at the rate of 84 g a.i./ha (120 g product/ha) for Assail Brand 70 WP Insecticide. Additional data are required for Assail Brand 70 WP Insecticide to establish the lowest effective rate for this use. The same proposed use claim is fully supported for Pristine Brand RTU Insecticide (a domestic, RTU product) based on the efficacy data of Assail and Pristine formulations.

Colorado potato beetle (on field tomato)
Ten trials conducted in 1996–1999 with acetamiprid in three Canadian provinces (Manitoba, Ontario, Quebec) and in four northern U.S. states (Idaho, Massachusetts, New York, Oregon) showed that both Assail Brand 70 WP Insecticide and Pristine Brand RTU Insecticide were effective in controlling Colorado potato beetle (CPB) in potato and tomato.

Performance at several rates (14, 28, 39, 56 and 84 g a.i./ha) of acetamiprid was compared with commercial standard insecticides including azinphos methyl, imidacloprid or cyhalothrin lambda and an untreated control. Of the rates tested, the rate of 56 g a.i./ha is optimal for control of both small and large larvae of CPB immediately after treatment and for up to 14 days after treatment (DAT). Data provided did not support the recommendation for use of higher rates at heavy pest pressure, as performance was not better than at the rate of 56 g a.i./ha. No evidence indicated that a range of rates was required to provide optimum control under varying population pressure or conditions.

One or two well timed foliar applications per generation of CPB should be sufficient to provide adequate control of CPB with Assail Brand 70 WP Insecticide. Another cloronicotinyl insecticide, imidacloprid, is limited to a maximum of two foliar applications per season to facilitate CPB resistance management and this restriction is required for acetamiprid as well.

To conclude, efficacy data fully support the proposed use claim for control of CPB on tomato for both Pristine Brand RTU Insecticide and Assail Brand 70 WP Insecticide (at the rate of 56 g a.i. or 80 g product/ha).

Aphids (on pome fruits)

Results were submitted from 6 field trials conducted in 1996 and 1998 that assessed the efficacy of Assail Brand 70 WP Insecticide for control of aphids on apples. The trials were conducted in Michigan (1 trial), Pennsylvania (2 trials), West Virginia (2 trials) and Washington (1 trial). The target species were rosy apple aphid, green apple aphid and spirea aphid. The performance of acetamiprid was compared with that of Provado (imidacloprid), a commercial standard insecticide treatment. Efficacy was assessed by recording the incidence of infestation (e.g., percentage of leaves or terminals that were infested) and (or) the severity of infestation (e.g., number of aphids per most infested leaf or terminal).

Sufficient efficacy data were submitted to allow for an assessment of the efficacy of acetamiprid for control of aphids on pome fruit. In the submitted studies with rosy apple aphid, acetamiprid applied at rates of 56 g a.i./ha significantly reduced aphid populations and performed as well as higher rates of application and the standard imidacloprid treatment. In one of the trials with a high population of spirea aphid, treatment at 56 g a.i./ha significantly reduced aphid populations compared with the untreated check, but did not perform as well as higher rates of application or the imidacloprid check. In neither trial did the 112 g a.i./ha application rate provide an improvement in control over the 84 g a.i./ha rate. Therefore, the submitted results do not demonstrate the need for rates of application higher than 84 g a.i./ha. Unless the applicant can provide further efficacy data to justify higher rates of application, the highest recommended label rate for control of aphids should be restricted to 84 g a.i./ha, with the higher rate being recommended for control of higher populations. Since the lowest rate tested was 56 g a.i./ha, which worked as well as higher rates in most trials, the lowest effective rate cannot be determined based on the submitted data.

To conclude, the proposed use claim for control of aphid on pome fruits is acceptable for Assail Brand 70 WP Insecticide at the rate of 56–84 g a.i./ha, with the higher rate being recommended for control of high populations. Additional data are required for Assail Brand 70 WP Insecticide to establish the lowest effective rate for this use. The same use claim is fully supported for Pristine Brand RTU Insecticide (a domestic, RTU product) based on the efficacy data of Assail Brand 70 WP Insecticide.

Tentiform leafminer (on pome fruits)

Results were submitted from 14 field trials conducted in 1996–1999 that assessed the efficacy of Assail Brand 70 WP Insecticide for control of tentiform leafminer on apples. The trials were conducted in Ontario (1 trial), Michigan (1 trial), New York (2 trials), Washington (6 trials), Pennsylvania (3 trials), and West Virginia (1 trial). The trials conducted in Washington evaluated efficacy against the western tentiform leafminer. All other trials were conducted with the spotted tentiform leafminer. The performance of acetamiprid was compared with that of a commercial standard insecticide treatment, either Guthion (azinphos methyl) or Provado (imidacloprid). Efficacy was assessed by comparing foliar damage levels between treated and untreated plots.

Results from the submitted studies show that acetamiprid provided very good control of both western tentiform leafminer and spotted tentiform leafminer when applied at rates of application ranging from 56 to 168 g a.i./ha. Treatments with acetamiprid reduced the number of mines by averages of 91.5, 91.6, 88.3, 96.8 and 71.7% compared with the untreated check for application rates of 56, 85, 120, 140 and 168 g a.i./ha, respectively. Statistically there was no difference in performance among any of the rates of application for acetamiprid tested, or the commercial standard (imidacloprid), in trials that directly compared the performance of these treatments. Based on the submitted data, the label rate of application for tentiform leafminer should be restricted to 56 g a.i./ha.

To conclude, the proposed use claim for control of tentiform leafminer on pome fruits is acceptable at the rate of 56 g a.i./ha for Assail Brand 70 WP Insecticide. Additional data are required for Assail Brand 70 WP Insecticide to establish the lowest effective rate for this use. The same use claim is fully supported for Pristine Brand RTU Insecticide (a domestic, RTU product) based on the efficacy data of Assail Brand 70 WP Insecticide.

Leafhoppers (on pome fruits)

Results were submitted from 9 field trials conducted in 1996–1998 that assessed the efficacy of Assail Brand 70 WP Insecticide for control of white apple leafhopper on apples. The trials were conducted in Michigan (1 trial), New York (1 trial), Washington (6 trials) and Pennsylvania (1 trial). The performance of acetamiprid was compared with that of a commercial standard insecticide treatment (imidacloprid). Efficacy was measured by recording the number of leafhoppers per leaf or terminal, or by conducting a visual assessment of leafhopper damage to leaves.

Sufficient efficacy data have been submitted to allow for an assessment of the efficacy of acetamiprid for control of white apple leafhopper on pome fruit. Leafhopper populations and (or) damage were reduced by averages of 73.8, 92.3, 98.5 and 100% compared with the untreated check for acetamiprid applied at rates of 56, 84, 112 and 168 g a.i./ha, respectively. Since the experimental protocols and population pressures for leafhopper differed among the trials (e.g., not all trials tested all rates of application for acetamiprid), the average percent control values alone do not provide adequate assessment of the relative performance of the different rates of application for acetamiprid when compared with the untreated check or the commercial standard treatment. Statistically there was no difference in performance among any of the rates of application for acetamiprid tested or the commercial standard (imidacloprid) in trials that directly compared the performance of these treatments. Therefore, unless the applicant can provide additional efficacy data to justify the need for higher rates of application, the label rate for application for leafhopper should be restricted to 56 g a.i./ha.

White apple leafhopper was the only species of leafhopper for which data were submitted for apples. Although no data were provided for other species of leafhopper on apples (e.g., potato leafhopper), results from studies conducted with leafhoppers on other crops (e.g., grape leafhopper, variegated leafhopper, Virginia leafhopper on grapes) suggest that

acetamiprid is also effective against other species of leafhoppers. Therefore, the general label for "leafhoppers" on apples is acceptable.

To conclude, the efficacy data fully support the proposed use claim for control of leafhoppers on pome fruit at the rate of 56 g a.i./ha for Assail Brand 70 WP Insecticide. The same use claim is fully supported for Pristine Brand RTU Insecticide (a domestic, RTU product) based on the efficacy data of Assail Brand 70 WP Insecticide.

Codling moth (on pome fruits)

Results were submitted from 16 field trials conducted in 1996–1999 that assessed the efficacy of Assail Brand 70 WP Insecticide for control of codling moth on apples. The trials were conducted in Ontario (2 trials), Nova Scotia (1 trial), Ohio (1 trial), Michigan (1 trial), New York (1 trial), Washington (9 trials) and Pennsylvania (1 trial). The performance of acetamiprid was compared with that of a commercial standard insecticide treatment for codling moth (primarily azinphos methyl). Treatments were timed specifically for control of codling moth based on results from pheromone trapping and use of degree-day models for predicting insect development. Efficacy was assessed by recording damage to fruit caused by codling moth following treatment. Damage assessments were conducted following the first and (or) second generation of codling moth.

Fruit damage caused by codling moth was reduced by averages of 67.8, 69.5, 74.9, 87.3, 77.5 and 78.5% compared with the untreated check for treatments with acetamiprid at rates of 47, 84, 112, 120, 140 and 168 g a.i./ha, respectively. However, since the experimental protocols and population pressures for codling moth differed among the trials and, not all trials tested each rate of acetamiprid, the average percent control values alone do not provide an accurate assessment of the relative performance of the different rates of application for acetamiprid when compared with the untreated check or the commercial standard treatment. Although all rates of application tested reduced codling moth damage compared with the untreated check, rates lower than 120 g a.i./ha did not perform consistently as well as did the commercial organophosphate treatment for codling moth (azinphos methyl) in all trials with very high population pressures. Treatments of acetamiprid at rates of 140–168 provided comparable levels of control to the commercial standard treatment in most trials. Therefore, the proposed label rate of 84–168 g a.i./ha is supported by the submitted studies. The 84 g a.i./ha rate should be the standard label rate of application for acetamiprid for codling moth. The 168 g a.i./ha rate should be recommended for very high populations only.

To conclude, the efficacy data fully support the proposed use claim for control of codling moth on pome fruits at the proposed rate of 84–168 g a.i./ha for Assail Brand 70 WP Insecticide, with the higher rate being recommended for control of high populations.

Pear psylla (on pome fruits)

Results were submitted from 4 field trials conducted in 1999 that assessed the efficacy of Assail Brand 70 WP Insecticide for control of pear psylla on pears. The trials were

conducted in Ontario (2 trials), Michigan (1 trial) and Washington (1 trial). The performance of acetamiprid was compared with that of a commercial standard insecticide treatment, either Agri-Mek (abamectin) or Mitac (amitraz). Efficacy was measured by recording the number of nymphs per leaf cluster in treated and untreated plots.

Sufficient efficacy data have been submitted to support the proposed use of acetamiprid for control of pear psylla on pears. Although all rates of acetamiprid tested (47–168 g a.i./ha) appeared to provide good knockdown in number of nymphs at 3–7 days after application (68–100% knockdown), higher rates of application (112 and 168 g a.i./ha) appeared to provide longer residual control in some trials. In one of the trials, only the 168 g a.i./ha rate reduced numbers of nymphs compared with the untreated check at 14 days after application. Application rates of 112–168 g a.i./ha performed statistically as well as did the abamectin or amitraz standard treatments. Lower rates of acetamiprid (47–85 g a.i./ha did not perform consistently as well as the standard treatments (e.g., at 3 weeks after treatment).

The proposed label rate for control of pear psylla (47–168 g a.i./ha) appears to be supported by the submitted studies, but the data do not demonstrate when the higher rates of application would be warranted. The draft label recommends that the higher rate of application be used for higher pest pressures. However, this recommendation is not supported by the submitted data. In the trial where the 168 g a.i./ha rate appeared to perform better than the lower rates, the pest pressure was not exceptionally high, and was not higher than that in the other submitted trials.

To conclude, the proposed use claim for control of pear psylla on pome fruits is accepted for Assail Brand 70 WP Insecticide at the proposed rate of 47–168 g a.i./ha, with the higher rate being recommended for control of high populations. Additional data are required to confirm the need and criteria for use of higher label rates (i.e., 168 g a.i./ha).

Leafhoppers (on grapes)

Results were submitted from 11 field trials conducted in 1996–1999 that assessed the efficacy of Assail Brand 70 WP Insecticide for control of leafhopper on grapes. The trials were conducted in Ontario, Michigan, New York, British Columbia, Washington and California. The performance of acetamiprid was compared with that of a commercial standard insecticide treatment (azinphos methyl, carbaryl or imidacloprid). Efficacy was measured by recording the number of leafhopper nymphs and (or) adults per leaf or group of leaves.

Sufficient efficacy data have been submitted to allow for an assessment of the efficacy of acetamiprid for control of leafhoppers on grapes. All rates of acetamiprid tested provided very good knockdown of leafhopper adults and nymphs. Mean percent control of adults at 6–10 DAT was 86.9 and 100% for application rates of 37–39 and 56 g a.i./ha, respectively. Mean percent control of nymphs at 6–10 DAT was 89.3, 99.7 and 100% for application rates of 37–39, 56 and 84 g a.i./ha, respectively. Generally, control was maintained for up to 20–28 DAT (the latest assessment date reported following

treatment). Statistically, rates of 37–39 g a.i./ha did not consistently provide good knockdown or residual control of nymphs compared with higher rates of acetamiprid or the standard treatment in all trials. The 56 g a.i./ha rate of acetamiprid provided excellent control, equivalent to that of the commercial standard, in all trials. There was no significant improvement in performance of acetamiprid when applied at rates higher than 56 g a.i./ha compared with the 56 g a.i./ha rate.

To conclude, the efficacy data fully support the proposed use claim for control of leafhoppers on grapes at the proposed rate of 56 g a.i./ha for Assail Brand 70 WP Insecticide.

USC 6 and USC 27: greenhouse non-food crops and outdoor ornamentals

Aphids

Results from 12 trials (5 greenhouse, 7 field) conducted in Oregon, New York, Hawaii, Indiana, Michigan, Ohio, California and Colorado from 1996 to 1998 were submitted to support the use of Chipco Brand Tristar 70 WSP Insecticide for the control of aphids. The trials were carried out on greenhouse plants (chrysanthemum, impatiens and hibiscus) and field ornamentals (crab apple, easter lily, rose and ginger). Target species included green apple aphid, melon aphid and green peach aphid. The most commonly tested rates were 28, 56, 84 and 112 g a.i./ha.

The efficacy data showed that Chipco Brand Tristar 70 WSP Insecticide provided equally effective control (80–100%) of aphids at a rate range of 28–112 g a.i./ha. Acetamiprid performed as well or better than the standard treatments (imidacloprid and acephate). The lowest effective rates for which there is substantial data are 0.0015 and 0.003% acetamiprid. Using a maximum spray volume of 2000 L/ha, these values translate into a per hectare maximum of approximately 28 g acetamiprid (i.e., the lowest rate that showed consistent performance). In other words, 28 g acetamiprid (2.5 packets of Tristar) mixed into 1000 L or 2000 L of water would provide the desired per hectare rates of application (0.0014–0.0028% acetamiprid).

To conclude, the efficacy data fully support the proposed use claim for control of aphids on lathhouse, shadehouse, greenhouse and outdoor non-food flowering and ornamental plants for Chipco Brand Tristar 70 WSP Insecticide at the rate of 28 g a.i./1000 L spray volume. The same pest claim is fully acceptable for Pristine Brand RTU Insecticide (a domestic, RTU product) based on the efficacy data of Chipco Brand Tristar 70 WSP Insecticide.

Whitefly

Results from 13 trials (12 greenhouse, 1 field) conducted in Ohio, California, Michigan, Florida and Texas between 1995 and 1999 were submitted to support the use of Chipco Brand Tristar 70 WSP Insecticide for the control of whitefly. The trials were carried out on greenhouse plants (chrysanthemum, poinsettia, gerbera, salvia and hibiscus) and field

ornamentals (rainbow aster). Target species included silverleaf whitefly, sweet potato whitefly and greenhouse whitefly.

The efficacy data showed that Chipco Brand Tristar 70 WSP Insecticide can control whitefly on greenhouse plants and outdoor ornamentals, although degree of performance varied among the trials. For control of adult whitefly, acetamiprid was sometimes better than, sometimes worse than and sometimes equal to imidacloprid. For control of immature whitefly, acetamiprid was generally poorer than or equivalent to imidacloprid. In terms of control of all stages of whitefly, acetamiprid was better than or similar to acephate. There was evidence that the rate of 56 g acetamiprid was more efficacious than 28 g acetamiprid, and that 112 and 84 g acetamiprid were sometimes more efficacious than 56 g acetamiprid.

It is concluded that the efficacy data fully support the proposed use claim for control of whitefly on lathhouse, shadehouse, greenhouse and outdoor non-food flowering and ornamental plants for Chipco Brand Tristar 70 WSP Insecticide at the proposed rate of 56–112 g a.i./1000 L spray volume. The same pest claim is fully acceptable for Pristine Brand RTU Insecticide (a domestic, RTU product) based on the efficacy data of Chipco Brand Tristar 70 WSP Insecticide.

European pine sawfly

One trial assessing efficacy of Chipco Brand Tristar 70 WSP Insecticide against European pine sawfly (EPS) was carried out on Mugo pine in Ohio in 1997. There were three application rates (28, 56 and 84 g acetamiprid/ha) in addition to untreated control and a commercial standard (carbaryl at 960 g/ha). Infested terminals were tagged and the number of larvae (living and dead) per terminal was counted both before and after treatment.

A single application of acetamiprid provided effective control of substantial infestations of EPS on Mugo pine. Control by acetamiprid of larval EPS was 98–100% at 24 h after application, and was similar to control by carbaryl (100%). There were little differences among rates of application (28, 56 and 112 g acetamiprid/ha). Data were not adequate to determine the lowest effective rate.

To conclude, the proposed use claim for control of EPS on lathhouse, shadehouse, greenhouse and outdoor non-food flowering and ornamental plants is acceptable for Chipco Brand Tristar 70 WSP Insecticide at the rate of 28 g a.i./1000 L. Additional data are required for Chipco Brand Tristar 70 WSP Insecticide to establish the lowest effective rate for this use. The same pest claim is fully supported for Pristine Brand RTU Insecticide (a domestic, RTU product) based on the efficacy data of Chipco Brand Tristar 70 WSP Insecticide.

Tentiform leafminer

Based on the efficacy data of Assail Brand 70 WP Insecticide (USC 14: terrestrial food crops, tentiform leafminer), the use claim for control of tentiform leafminer on lathhouse,

shadehouse, greenhouse and outdoor non-food flowering and ornamental plants is acceptable for Chipco Brand Tristar 70 WSP Insecticide at the rate of 56 g a.i./1000 L. Additional data are required for Chipco Brand Tristar 70 WSP Insecticide to establish the lowest effective rate for this use. The same use claim is fully supported for Pristine Brand RTU Insecticide (a domestic, RTU product) based on the efficacy data of Assail Brand 70 WP Insecticide.

Leafhoppers

The proposed use claim for control of leafhoppers on outdoor ornamentals is fully supported for Pristine Brand RTU Insecticide (a domestic, RTU product) and the use claim for control of leafhoppers on lathhouse, shadehouse, greenhouse and outdoor non-food flowering and ornamental plants is fully supported for Chipco Brand Tristar 70 WSP Insecticide (at the rate of 56 g a.i./1000 L) based on the efficacy data of Assail Brand 70 WP Insecticide (USC 14: terrestrial food crops, leafhoppers).

7.1.5 Seasonal maximum number of applications and rate per crop site

The number of applications and the total application rate required for crop protection per season per crop site depend on overall seasonal pest problems. Restriction on seasonal maximum number of application and rate per crop site can be used for insecticide resistance management. The seasonal maximum rate allowed for a crop site can not exceed the limit set by multiplying the approved maximum single application rate on a crop site by the approved maximum number of applications on that crop site.

Since some approved application rates are lower than the proposed application rates for some uses, the proposed seasonal maximum application rate for certain crop sites should be modified accordingly. The required label changes are specified as follows.

For Assail Brand 70 WP Insecticide: (1) the seasonal maximum application rate for leafy vegetables should be 430 g product or 300 g a.i. per hectare; (2) although a seasonal maximum of four applications is allowed on tomato, number of applications for control of CPB should be limited to a maximum of two foliar applications per season to facilitate CPB resistance management, which is required for imidacloprid, another cloronicotinyl insecticide.

For Chipco Brand Tristar 70 WSP Insecticide: a seasonal maximum of five applications is allowed on outdoor flowering and ornamental plants, and a yearly maximum of two applications is allowed for non-food flowering and ornamental plants in greenhouse, shadehouse and lathhouse. The yearly maximum application rate should be limited to 20 packs of product or 224 g a.i. per hectar for the uses in greenhouse, shadehouse and lathhouse and 50 packs of product or 560 g a.i. per hectare for outdoor uses.

7.2 Phytotoxicity to target plants (including different cultivars) or to target plant products

Phytotoxicity was not reported in any of the field efficacy trials on the proposed plants associated with the use of Assail Brand 70 WP Insecticide, Chipco Brand Tristar 70 WSP and Pristine Brand RTU Insecticide.

7.3 Observations on undesirable or unintended side effects, e.g., on beneficial and other non-target organisms, on succeeding crops, other plants or parts of treated plants used for propagating purposes (e.g., seed, cutting, runners)

N/A

7.3.1 Impact on succeeding crops

N/A

7.3.2 Impact on adjacent crops

N/A

7.4 Economics

Not assessed.

7.5 Sustainability

7.5.1 Survey of alternatives

The major alternative insecticide active ingredients currently registered for control of the pests on any of the proposed labels of the acetamiprid products include, but are not necessarily limited to, the following:

Pest	Available alternative active ingredients
Aphids	carbamates (methomyl, pirimicarb), neonicotinoids (imidacloprid), organochlorines (endosulfan), organophosphates (acephate, azinphos methyl, diazinon, dimethoate, malathion, oxydemeton methyl), pyrethroids (deltamethrin), dormant oil
Whitefly	carbamates (bendiocarb, carbaryl, pirimicarb), insect growth regulators (kinoprene), organochlorine (endosulfan, methoxychlor), organophosphates (acephate, chlorpyrifos, diazinon, dichlorvos, dimethoate, malathion, naled, oxydemeton methyl, sulfotep), pyrethroids (*d-trans* allethrin, permethrin, *d*-phenothrin, pyrethrins, resmethrin, tetramethrin), dicofol, dormant oil, insecticidal soaps, rotenone

Pest	Available alternative active ingredients
Colorado potato beetle	carbamates (carbaryl, carbofuran, oxamyl), microbials (*Bacillus thuringiensis*), neonicotinoids (imidacloprid), organochlorines (endosulfan, methoxychlor), organophosphates (azinphos methyl, chlorpyrifos, diazinon, malathion, methamidophos, methidathion, naled, phorate, phosmet), pyrethroids (cyhalothrin-lambda, cypermethrin, deltamethrin, fenvalerate, permethrin)
Tentiform leafminer	avermectin (abamectin), carbamates (carbaryl, methomyl, oxamyl), neonicotinoids (imidacloprid), organophosphates (diazinon, phosmet), pyrethroids (permethrin, cypermethrin, deltamethrin, cyhalothrin-lambda), benzoic acid hydrazide (tebufenozide)
Leafhoppers	carbamates (carbaryl, formetanate hydrochloride, methomyl, oxamyl, pirimicarb), organophosphates (acephate, azinphos-methyl, chlorpyrifos, diazinon, dimethoate, disulfoton, malathion, naled, parathion, phosalone, phosmet), organochlorines (endosulfan, methoxychlor), pyrethroids (cypermethrin, cyhalothrin-lamda, deltamethin, *d*-phenothrin, permethrin, resmethrin), pyrethrins, botanical (rotenone)
Codling moth	carbamates (carbaryl, methomyl), organophosphates (azinphos-methyl, diazinon, dichlorvos, dimethoate, malathion, parathion, phosalone, phosmet), organochlorines (endosulfan), pyrethroids (cyhalothrin-lamda, cypermethrin, deltamethrin, permethrin), pheromone
Psylla	amidine (amitraz), avermectin (abamectin), carbamates (carbaryl), chinomethionat, mancozeb, mineral oil, organophosphates (axinphos-methyl, diazinon, dimethoate, malathion, phosalone, phosmet), organochlorines (endosulfan), pyrethroids (cyhalothrin-lamda, cypermethrin, deltamethrin, permethrin), pyrethrins, pyridaben, soap
European pine sawfly	organophosphates (chlorpyrifos, diazinon)

7.5.2 Contribution to risk reduction

Acetamiprid is potentially an alternative to organophosphate insecticides for control of the pests on the proposed labels of Assail Brand 70 WP Insecticide, Chipco Brand Tristar 70 WSP Insecticide and Pristine Brand RTU Insecticide. Organophosphate insecticides are currently undergoing re-evaluation by the PMRA and the U.S. EPA.

7.5.3 Information on the occurrence or possible occurrence of the development of resistance

Acetamiprid is a broad spectrum insecticide that belongs to a new class of compounds, the neonicotinoids. Neonicotinoids are believed to interfere with the nicotinic acetylcholine receptors of the insect's nervous system, although different compounds may have specific binding site(s) or receptor(s). Other neonicotinoid insecticides currently registered in Canada include imidacloprid and thiamethoxam. According to Regulatory

Directive DIR99-06, *Voluntary Pesticide Resistance Management Labelling Based on Target Site/Mode of Action*, the following statements should be incorporated on the labels of Assail Brand 70 WP Insecticide and Chipco Brand Tristar 70 WSP Insecticide, which are for agricultural uses.

GROUP	4	INSECTICIDE

Resistance management recommendations
For resistance management, this is a Group 4 (neonicotinoid) insecticide. Any insect population may contain individuals naturally resistant to this product and other Group 4 insecticides. The resistant biotypes may dominate the insect population if these insecticides are used repeatedly in the same field. Other resistance mechanisms that are not linked to site of action, but specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance management strategies should be followed.

To delay insecticide resistance:

- Where possible, rotate the use of this product with different groups that control the same pests.
- Use tank mixtures with insecticides from a different group when such use is permitted.
- Insecticide use should be based on an integrated pest management (IPM) program that includes scouting and record keeping and considers cultural, biological and other chemical control practices.
- Monitor treated pest populations for resistance development.
- Contact the local extension specialist or certified crop advisors for any additional pesticide resistance-management and IPM recommendations for the specific site and pest problems in the area.
- For further information or to report suspected resistance, contact (company representatives) at (toll free number) or at (Internet site).

7.6 Conclusions

For Assail Brand 70 WP Insecticide: adequate efficacy and value data fully support the label claims for control of CPB (on tomato), codling moth (on pome fruits) and leafhopper (on pome fruits and grapes). Although the following use claims are acceptable, efficacy data were not adequate to determine the lowest effective application rate (LER) for control of aphids (on field tomato, leafy vegetables, cole crops and pome fruits), whitefly (on tomato and cole crops) and tentiform leafminer (on pome fruits). Therefore, additional data are required to demonstrate LERs for these uses. Additional data are also required to justify using high application rates for control of pear psylla on pome fruits.

For Chipco Brand Tristar 70 WSP Insecticide: Adequate efficacy and value data fully support the label claims for control of aphids, whitefly and leafhoppers on lathhouse, shadehouse, greenhouse and outdoor non-food flowering and ornamental plants. Although the following use claims are acceptable, efficacy data were not adequate to determine LERs for control of EPS and tentiform leafminer on lathhuse, shadehouse, greenhouse and outdoor flowering and ornamental plants. Therefore, additional data are required to demonstrate LERs for these uses.

For Pristine Brand RTU Insecticide: adequate efficacy and value data fully support the label claims for domestic uses to control aphids (on field tomato, leafy vegetables, cole crops, pome fruits and outdoor ornamental and flowering plants), whitefly (on field tomato, cole crops and outdoor ornamental and flowering plants), CPB (on field tomato), leafhopper (on pome fruits and outdoor flowering and ornamental plants), tentiform leafminer (on pome fruits and outdoor flowering and ornamental plants) and EPS (on outdoor flowering and ornamental plants).

The registrant provided adequate data to support the registration of crops in the leafy vegetable crop group 4: amaranth leafy, arugula, cardoon, celery, celery (Chinese), celtuce, chervil, chrysanthemum (edible-leaved), chrysanthemum (garland), corn salad, cress (garden), cress (upland), dandelion leaves, dock, endive, fennel (Florence), lettuce (head and leaf), orach, parsley leaves, purslane (garden), purslane (winter), radicchio, rhubarb, spinach, spinach (New Zealand), spinach (vine), Swiss chard; the cole crop group 5: broccoli, broccoli (Chinese), broccoli raab, Brussels sprouts, cabbage, cabbage (Chinese, bok choy), cabbage (Chinese, napa), cabbage (Chinese mustard, gai choy), cauliflower, cavalo broccolo, collards, citrus (dried pulp), kale, kohlrabi, mizuna, mustard greens, mustard spinach, rape greens, and the pome fruit crop group 11: apple, crabapple, pear, pear (oriental) and quince.

8.0 Toxic Substances Management Policy

During the review of acetamiprid insecticide and the end-use products Pristine Brand RTU, Chipco Brand Tristar 70 WSP and Assail Brand 70 WP, the PMRA has considered the implications of the federal Toxic Substances Management Policy[1] and the PMRA Regulatory Directive DIR99-03[2] and has concluded the following:

The TSMP criteria for persistence of acetamiprid and major transformation products IM-1-4, IM-1-2 and IC-0 is not exceeded. The persistence and mobility in soil of the major

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1 The federal Toxic Substances Management Policy is available through Environment Canada's Web Site at www.ec.gc.ca/toxics.

2 The PMRA's *Strategy for Implementing the Toxic Substances Management Policy*, DIR99-03, is available through the Pest Management Information Service: Phone 1-800-267-6315 within Canada or 1-613-736-3799 outside Canada (long distance charges apply); Fax (613) 736-3798; E-mail pminfoserv@hc-sc.gc.ca or through our website at www.hc-sc.gc.ca/pmra-arla.

transformation product IM-1-5, however, is unknown. The value for half-life of acetamiprid technical in soil (17 days) and water (45 days) is below the TSMP Track-1 cut-off criteria for soil and water (≥ 182 days). Acetamiprid is unlikely to volatilize, based on its low vapour pressure. Therefore, a study of persistence in air is not triggered. Persistence of the major transformation products IM-1-4 in the sediment and of IB-1-1 in water are unknown.

Acetamiprid is not bioaccumulative. Studies have shown that the octanol–water partitioning coefficient (log K_{ow}) is 0.8, which is below the TSMP Track-1 cut-off criterion of ≥5.0. Therefore, a study of bioaccumulation in bluegill sunfish is not triggered. No evidence of accumulation of the parent compound or its metabolites was observed in the mammalian metabolism studies.

The toxicity of acetamiprid is described in Sections 3.0 and 6.0.

Acetamiprid does not contain any byproducts or microcontaminants known to be Track-1 substances. Impurities of toxicological concerns are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

The formulated products do not contain any formulants that are known to contain TSMP Track-1 substances.

9.0 Overall conclusions

Product chemistry

The product chemistry data for Acetamiprid used in the three end-use products, Assail Brand 70 WP Insecticide, Chipco Brand Tristar 70 WSP Insecticide and Pristine Brand RTU Insecticide are complete. The technical material was fully characterized and the specifications were supported by the analysis of five batches for active and impurities using specific validated methods of analysis. Based on the starting materials and the manufacturing process used, the technical material does not contain any TSMP Track-1 substances as identified in Appendix II of DIR99-03. The required physical and chemical properties of the technical material have been provided. With the exception of the storage stability data to support stability claim, all of the chemical and physical properties applicable to the basic and alternate formulations have also been provided or are not applicable. Two HPLC methods for the determination of the active in the four formulations were submitted and were assessed to be suitable for use as enforcement analytical methods.

Impact on human and animal health

Technical acetamiprid is highly acutely toxic via the oral route of exposure; the commercial formulations containing 70% acetamiprid are moderately toxic via the oral route of exposure and the domestic product, Pristine Brand RTU Insecticide is of low toxicity via the oral route of exposure. In acute dermal toxicity studies, the technical material and all of the end-use products were of low toxicity; in acute inhalation studies

technical acetamiprid was slightly toxic and the end-use products were of low toxicity. All were minimally irritating to the eye, the technical was non-irritating to the skin, the 70% formulations were minimally irritating to the skin and Pristine Brand RTU Insecticide was slightly irritating to the skin. The sensitization studies all yielded negative responses.

Acetamiprid was rapidly absorbed, widely distributed to the tissues, extensively and rapidly metabolized, and rapidly excreted, predominantly in the urine. In subchronic and chronic toxicity studies in rats, mice and dogs, acetamiprid did not induce any specific target organ toxicity. Generalized toxicity was observed in rats, mice and dogs as decreases in body weight, body weight gain, food consumption and (or) food efficiency. Mild liver effects were noted in several studies, which were considered to be indicative of an adaptive response to treatment, and were not deemed to be adverse.

Acetamiprid is not considered to be genotoxic or carcinogenic. There was no evidence of teratogenicity in the developmental toxicity studies. In acute and subchronic neurotoxicity studies, treatment with acetamiprid did not result in any neuropathology.

Acetamiprid is an insect neurotoxicant. Clinical signs of neurotoxicity were observed in acute toxicity studies and there was qualitative evidence of increased susceptibility of the young in the two-generation reproductive toxicity study; however, the observations that are suggestive of increased susceptibility required prolonged exposure to be observed. Based on these considerations, an additional SF of 3 is applied to chronic dietary and occupational exposure scenarios.

Occupational and bystander exposure

Pristine Brand RTU: Based on a surrogate application study and Tier 1 exposure estimates, acceptable MOEs were derived for applicator exposure and postapplication exposure, including youth.

Assail Brand 70 WP: Based on PHED exposure estimates and the maximum application rate, MOEs are acceptable for mixing/loading/applying Assail Brand 70 WP to all proposed crops. Postapplication exposure was estimated using Tier 1 assumptions, the maximum application rate, and the maximum number of applications applied at the minimum spray interval. MOEs for re-entry workers are acceptable for all proposed uses.

Chipco Brand Tristar 70 WSP: Based on PHED exposure estimates and the maximum label rate, MOEs are acceptable for mixing/loading/applying Chipco Brand Tristar 70 WSP to outdoor and greenhouse ornamentals.

Postapplication exposure was estimated using Tier 1 assumptions, the maximum application rate and the maximum number of applications applied at the minimum spray interval. For outdoor ornamentals, a daily dissipation rate of 10% was assumed. For ornamentals grown in greenhouses, shadehouses or lathhouses there is no default dissipation rate and no data was submitted. In the absence of data, it is assumed that there

is no dissipation. For all proposed uses of Chipco, MOEs for postapplication exposure are acceptable at the maximum application rates.

Residues

Sufficient representative data was submitted to support a temporary registration on the crops of crop group 4 (the leafy vegetables), crop group 5 (the Brassica vegetables), crop group 11 (the pome fruits), tomatoes and grapes. Additionally, MRLs will be promulgated to cover the residues of acetamiprid in the remaining imported fruiting vegetables crops (crop group 8), citrus fruit (crop group 10) and cotton. The consumption estimates coupled with the MRLs indicated that there is adequate protection of the consumer, including infants, children, adults and seniors, from dietary residues of acetamiprid following use in accordance with GAP.

Environmental assessment

Acetamiprid is slightly persistent in aerobic but persistent in anaerobic aquatic systems. Acetamiprid is non-persistent to slightly persistent in soil and, therefore, no significant carryover of residues to the next field season is expected. Acetamiprid is not likely to leach through soil layers. However, acetamiprid has a potential for partitioning into the sediment. The principal routes of transformation are biotransformation in soil and in aquatic environments. It is not expected to volatilize from water and moist soils. The persistence and mobility of the major transformation products IM-1-5 and IB-1-1 are unknown.

Acetamiprid will pose a high risk to marine–estuarine invertebrates, such as the mysid shrimp, and a moderate risk to terrestrial plants. Acetamiprid is toxic to honeybees exposed to direct treatment. The risk to marine–estuarine organisms and terrestrial plants can be mitigated by the establishment of terrestrial and aquatic buffer zones. The risk to honeybees can be mitigated by precautionary label statement contraindicating application when bees present in the area to be treated.

Efficacy

For Assail Brand 70 WP Insecticide: Adequate efficacy and value data fully support the label claims for control of CPB (on field tomato), codling moth (on pome fruits) and leafhopper (on pome fruits and grapes). Although the following use claims are acceptable, efficacy data were not adequate to determine the LER for control of aphids (on field tomato, leafy vegetables, cole crops and pome fruits), whitefly (on field tomato and cole crops) and tentiform leafminer (on pome fruits). Therefore, additional data are required to demonstrate LERs for these uses. Additional data are also required to justify using high application rates for control of pear psylla on pome fruits.

For Chipco Brand Tristar 70 WSP Insecticide: Adequate efficacy and value data fully support the label claims for control of aphids, whitefly and leafhoppers on shadehouse, lathhouse, greenhouse and outdoor non-food flowering and ornamental plants. Although the following use claims are acceptable, efficacy data were not adequate to determine LERs for control of EPS and tentiform leafminer on shadehouse, lathhouse, greenhouse

and outdoor non-food flowering and ornamental plants. Therefore, additional data are required to demonstrate LERs for these uses.

For Pristine Brand RTU Insecticide: Adequate efficacy and value data fully support the label claims for domestic uses to control aphids (on field tomato, leafy vegetables, cole crops, pome fruits and outdoor flowering and ornamental plants), whitefly (on field tomato, cole crops and outdoor flowering and ornamental plants), CPB (on field tomato), leafhopper (on pome fruits and outdoor flowering and ornamental plants), tentiform leafminer (on pome fruits and outdoor flowering and ornamental plants) and EPS (on outdoor flowering and ornamental plants).

The company provided adequate data to support the registration of the crops in leafy vegetable crop group 4: amaranth leafy, arugula, cardoon, celery, celery (Chinese), celtuce, chervil, chrysanthemum (edible-leaved), chrysanthemum (garland), corn salad, cress (garden), cress (upland), dandelion leaves, dock, endive, fennel (Florence), lettuce (head and leaf), orach, parsley leaves, purslane (garden), purslane (winter), radicchio, rhubarb, spinach, spinach (New Zealand), spinach (vine), Swiss chard; in the cole crop group 5: broccoli, broccoli (Chinese), broccoli raab, Brussels sprouts, cabbage, cabbage (Chinese, bok choy), cabbage (Chinese, napa), cabbage (Chinese mustard, gai choy), cauliflower, cavalo broccolo, collards, citrus (dried pulp), kale, kohlrabi, mizuna, mustard greens, mustard spinach, rape greens, and in pome fruit crop group 11: apple, crabapple, pear, pear (oriental) and quince, for both Assail Brand 70 WP Insecticide and Pristine Brand RTU Insecticide.

10.0 Regulatory decision

The active ingredient acetamiprid and the associated end-use products, Assail Brand 70 WP Insecticide for control of aphid, Colorado potato beetle and whitefly on field tomato; aphid, codling moth, leafhopper, pear psylla and tentiform leafminer on pome fruits (crop group 11); leafhopper on grapes; aphid and whitefly on cole crops (crop group 5); aphid on leafy vegetables (crop group 4); Chipco Brand Tristar 70 WSP Insecticide for control of aphid, whitefly, leafhopper, European pine sawfly and tentiform leafminer on non-food greenhouse, lathhouse, shadehouse and outdoor uses on flowering and ornamental plants; and Pristine Brand RTU Insecticide for control of aphid, Colorado potato beetle and whitefly on field tomato; aphid, leafhopper and tentiform leafminer on pome fruits (crop group 11); aphid and whitefly on cole crops (crop group 5); aphid on leafy vegetables (crop group 4) and aphid, European pine sawfly, leafhopper, whitefly and tentiform leafminer on outdoor flowering and ornamental plants, have been granted temporary registration pursuant to Section 17 of the Pest Control Products Regulations, subject to the generation of the following studies:

- Storage stability data
- Postnatal developmental neurotoxicity study
- Independent laboratory validation (ILV) animal matrices
- Supervised field trials (residues)

- Freezer storage stability information from the limited crop rotation trials
- Persistence and mobility of the major transformation product IM-1-5 in soil
- Persistence of the major transformation product IM-1-4 in sediment
- Persistence of the major transformation product IB-1-1 in water
- Toxicity to earthworm
- Toxicity to bees and pollinators
- Toxicity to freshwater invertebrates (amphipod and aquatic insects)
- Chronic toxicity (early life stages) to fish
- Reproductive toxicity to bobwhite quail and mallard duck
- Toxicity to non-target plants
- Small-scale efficacy trials in the field

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List of abbreviations

ACN	acetonitrile
ADI	acceptable daily intake
a.i.	active ingredient
APCI	atmospheric pressure chemical ionization
ARfD	acute reference dose
BUN	blood urea nitrogen
bw	body weight
CAS	Chemical Abstracts Service
CPB	Colorado potato beetle
d	day
DAT	days after treatment
DCM	dichloromethane
DEEM™	Dietary Exposure Evaluation Model™
DNA	deoxyribonucleic acid
DRA	dietary risk assessment
DT_{50}	time required for non first-order 50% dissipation
EC_{25}	concentration effective against 25% of test organisms
EC_{50}	median effective concentration
ECD	electron capture detector
EEC	expected environmental concentration
EPA	Environmental Protection Agency
EPS	European pine sawfly
ESAD	Efficacy and Sustainability Assessment Division
F_1	first generation offspring
F_2	second generation offspring
FDA	*Food and Drugs Act*
FOB	functional observational battery
ft	foot
g	gram
GAP	Good Agricultural Practices
GC	gas chromatography
GD	gestation day
GGT	gamma glutamyl transpeptidase
GSD	geometric standard deviation
h	hour
ha	hectare
HAFT	highest average field trial
HDT	highest dose tested
HPLC	high performance liquid chromatography
ILV	independent laboratory validation
i.p.	intraperitoneal
IPM	integrated pest management
i.v.	intravenous

K_d	Freundlich adsorption coefficient (a.k.a. soil sorption coefficient; soil–water partition coefficient)
K_{oc}	organic carbon adsorption coefficient (a.k.a. organic carbon partition coefficient; soil sorption constant)
K_{ow}	*n*-octanol–water partition coefficient
K_{st}	dust explosion constant
lb	pound
LC	liquid chromatography
LCL	lower confidence limit
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LER	lowest effective rate
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOEC	lowest observable effect concentration
LOQ	limit of quantitation
MAS	maximum average score
MIS	maximum irritation score
MOE	margin of exposure
MOS	margin of safety
MRL	maximum residue level
MS	mass spectrometry
MTDB	maximum theoretical dietary burden
n	number
NOAEL	no observable adverse effect level
NOEC	no observable effect concentration
NOEL	no observable effect level
NZW	New Zealand White
PDI	potential daily intake
pH	potential hydrogen
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RAC	raw agricultural commodity
ROC	residue of concern
RSD	relative standard deviation
RTU	ready-to-use
SF	safety factor
TGAI	technical grade active ingredient
TLC	thin-layer chromatography
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UCL	upper certified limit
UF	uncertainty factor

U.S.	United States
USC	use–site category
UV	ultraviolet

Appendix I Methods for residue analysis

Table 1 Method for analysis of the active substance as manufactured

Product	Analyte	Method type	Analysis range (%)	Mean recovery (%)	RSD (%)	Method
Technical	Active	HPLC–UV at 254 nm	30.0–150.0	99.8	0.09	Acceptable
Technical	Major impurities	HPLC–UV at 254 nm	0.01–0.2	98.0–99.3	0.0–1.6	Acceptable

Table 2 Method for formulation analysis

Product[a]	Analyte	Method	Linearity range (µg/mL)	Recovery range (%) (*n*)	Standard deviation (*n*)	Method
I	Active	HPLC–UV at 255 nm	18.0 –150.0	100.0 ± 1.2 (3)	0.05% (3)	Acceptable
II		HPLC–UV at 245 nm	10.0–40.0	100.1 ± 1.0 (3)	0.70% (3)	Acceptable

[a] I. Assail Brand 70 WP insecticide; II. Pristine Brand RTU Insecticide

Appendix II Occupational exposure summary tables

Table 1 Exposure estimates and MOE for mixer/loader/applicators (target MOE = 100)

Exposure scenario (formulation and equipment)	Crop	Total exposure (mg a.i./kg bw/d)[a]	MOE[b]
Wettable powder and groundboom	Leafy vegetables	0.082	210
	Fruiting vegetables, cole crops	0.115	150
Wettable powder and airblast	Pome fruits	0.142	120
Wettable powder and airblast	Grapes	0.037	480
Wettable powder in water soluble bags and low pressure hand wand	Ornamentals, ornamental trees, non-bearing fruit and nut trees	0.003	6500
Wettable powder in water soluble bags and high pressure hand wand	ornamentals, ornamental trees, non-bearing fruit and nut trees	0.007	2600

[a] Used maximum application rate and area treated per day for each crop; dermal absorption value is 30%; body weight is 60 kg (based on average female body weight because of reproductive effects)

[b] MOE = NOAEL/daily dose (short- and intermediate-term NOAEL = 17.9 mg/kg/d)

Table 2 Short- and intermediate-term postapplication exposure and risk for acetamiprid on the day of the last application (target MOE = 100)

Crops	Application rate (g a.i./ha)	TC[a] (cm^2/h)	No. of applications	Spray interval (d)	DAA[b]	Daily dose (mg/kg/d)[c]	MOE[d]
Leafy vegetables	60	2 500	5	7	0	0.022	800
Fruiting vegetables	84	1 000	4	7	0	0.012	1460
Cole crops	84	5 000	5	7	0	0.063	280
Pome fruits	56	10 000	2	14	0	0.055	325
Outdoor ornamentals	168	3 000	4	12	0	0.056	320
Outdoor ornamentals	112	7 000	5	7	0	0.117	150
Ornamentals in shadehouses, lathhouses and greenhouses[e]	112	7 000	2	7	0	0.125	140

[a] TC, transfer coefficient for highest exposure activities for each specific crop

[b] DAA, days after last application

[c] Body weight is 60 kg (based on average female body weight because of reproductive effects)

[d] MOE = NOAEL/daily dose (short- and intermediate-term NOAEL = 17.9 mg/kg/d)

[e] Assume no dissipation in shadehouses, lathhouses or greenhouses.

Table 3 Short-term exposures and risks for residential uses of acetamiprid (target MOE = 300)

Exposure scenario	Total dose[a] (mg/kg/d)	MOE[b]
PHED aerosol application	0.000 144	124 000
RTU trigger pump spray	0.000 035	510 000

[a] Dermal absorption value = 30%; body weight is 60 kg (based on average female body weight because of reproductive effects)

[b] MOE = NOAEL/daily dose (short- and intermediate-term dermal NOAEL = 17.9 mg/kg/d)

Table 4 Dermal postapplication exposure and risk from pesticide residues on gardens and backyard trees (target MOE = 300)

Crops	TC[a] (cm^2/h)	No. of applications	Spray interval (d)	DAA[b]	Daily dose ($\mu g/kg/d$)[c]	MOE[d]
Adults (body weight = 60 kg)						
Leafy vegetables	2500	5	7	0	1	17 000
Fruiting vegetables	1000	5	7	0	0.4	44 000
Cole crops	5000	5	7	0	2	8 000
Pome fruits	3000	5	7	0	1.2	14 000
Outdoor ornamentals	7000	5	7	0	2.8	6 000
Youth (body weight = 39 kg)						
Leafy vegetables	1250	5	7	0	0.8	23 000
Fruiting vegetables	500	5	7	0	0.3	58 000
Cole crops	2500	5	7	0	1.5	11 000
Pome fruits	1500	5	7	0	0.9	19 000
Outdoor ornamentals	3500	5	7	0	2.2	8 000

[a] TC, transfer coefficient for highest exposure activities for each specific crop

[b] DAA, days after last application

[c] Body weight is 60 kg for adults (based on average female body weight because of reproductive effects) and 39 kg for youth; dermal absorption = 30%; application rate is 1 L container contains 0.06 g a.i. (0.32 $\mu g/cm^2$)

[d] MOE = NOAEL/daily dose (short- and intermediate-term NOAEL = 17.9 mg/kg/d)

Appendix III Toxicology summary tables

Table 1 Summary of the toxicity studies with acetamiprid

METABOLISM

Rate and extent of absorption and excretion: Rapid and complete absorption, predominant route of excretion was urine (76–97% within 24 h), independent of gender, dose or position of label; repeated dosing also resulted in rapid and complete urinary excretion within 24 h. Fecal excretion accounted for 5–17%, depending on position of radiolabel (12–17% of ring labelled after single oral or i.v. administration versus 5% of cyano-labelled material). In a separate biliary excretion study, approximately 19% of administered dose was excreted in the bile over 48 h, with no gender difference.

Distribution and target organ(s): Peak blood concentrations occurred withing 1–4 h of dosing; clearance from the blood was nearly complete within 48 h. Tissue half lives ranged from 3–8 h. Tissue burdens were low (generally <1% of administered dose); greatest amounts detected in GIT (including lumen contents) up to 3–4%. No gender differences observed, repeat dosing did not result in tissue sequestration of acetamiprid or its metabolites

Toxicologically significant compound(s): Extensively and rapidly metabolized, only 3–7% of the dose was recovered in urine and feces as parent. Metabolites accounted for 79–86% of administered dose. Slight increase in glycine conjugate following repeat dosing. Initial phase I demethylation resulted in major metabolite IM-2-1 (12–24% of administered dose); most prevalent metabolite (IC-O or 6-chloronicotinic acid, 24–28% of administered dose) results from removal of the cyanoacetamide group from demethylated IM-2-1.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/d)	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
ACUTE STUDIES: TECHNICAL			
Oral	Rat, Crj:CD(SD) 100, 150, 230, 340 or 510 mg/kg bw High mortality noted among ♀, separate study conducted at 80, 100, 120, 140 and 160 mg/kg bw	LD_{50} = 217 mg/kg bw (♂) LD_{50} = 146 mg/kg bw (♀) LD_{50} = 167 mg/kg bw (combined) NOAEL for clinical signs 100 mg/kg bw in ♂ 80 mg/kg bw in ♀	**Highly toxic**, clinical signs of toxicity included crouching, tremors, low sensitivity, lateral/prone position, urinary incontinence and ataxia. Normal appearance in all survivors by day 2. **DANGER POISON** **Skull and Cross bones in octagon**
Dermal	Rat, Crj:CD(SD) 2000 mg/kg bw	LD_{50} > 2000 mg/kg bw	**Low toxicity**, no clinical signs, no effect on body weights, no abnormal observations at necropsy
Inhalation	Rat, Crj:CD(SD) 0 or 1.15 mg/L Mass median aerodynamic diameter = 8.0 μm GSD = 2.71	LC_{50} > 1.15 mg/L	**Slightly toxic**, no mortality, clinical signs of toxicity included whole body tremors, brown staining around the eyes, hair loss from the body and in ♀, lethargy, clear discharge from snout.
Eye irritation	Rabbit, NZW 0.1 g	Maximum average score (MAS) = 0.2 Maximum irritation score (MIS) = 1.0 (1 h)	**Minimally irritating**
Skin irritation	Rabbit, NZW 0.5 g	MAS = 0 MIS = 0	**Non-irritating**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/d)	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Skin sensitization (Maximization test)	Guinea pig, Dunkin/Hartley	Non-sensitizing	**Non-sensitizing**
ACUTE STUDIES: METABOLITES			
Oral IC-0	Rat, Crj:CD(SD) 2000 or 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw	**Low toxicity**, no clinical signs, transient body weight loss in ♀ at 2000 and both sexes at 5000 mg/kg bw
Oral IM-0	Rat, Crj:CD(SD) 1000, 1500, 2000 or 3000 mg/kg bw Supplemental investigation one group of 5 ♀ dosed at 1300 mg/kg bw	LD_{50} = 1842 mg/kg bw (♂) LD_{50} = 1483 mg/kg bw (♀) LD_{50} = 1792 mg/kg bw (combined)	**Slight toxicity**, all deaths occurred within 2 days of dosing, clinical signs of toxicity included decline in righting reflex, decline in motor activity, hypotonea, prone position and ataxia. All signs absent by study day 2. Body weight loss in a few ♀ at 1300 and 1500 mg/kg bw.
Oral IM-1-2	Rat, Crj:CD(SD) 2000 or 5000 mg/kg bw	LD_{50} > 5000 mg/kg bw	**Low toxicity**, no clinical signs and no effect on body weight at 2000 mg/kg bw. Decreased spontaneous activity in 2 ♂ and 2 ♀ at 5000 mg/kg bw and 1 ♀ appeared hypothermic. Decreased body weight recorded in a few animals on study day 2. All animals appeared normal by study day 2.
Oral IM-2-1	Rat, Crl:CD BR; ♂ dosed at 0, 2000, 2500, 3000 or 5000 mg/kg bw; ♀ dosed at 0, 500, 1000, 1500, 2000 or 5000 mg/kg bw	LD_{50} = 2543 mg/kg bw (♂) LD_{50} = 1762 mg/kg bw (♀) LD_{50} = 2176 mg/kg bw (combined)	**Slightly toxic**, all deaths occurred within 3 days of dosing. Clinical signs included crouching, tremor, ptosis and hypothermia, and decedents exhibited lateral/prone position, tonic convulsions, lacrimation exophthalmos and clonic convulsion prior to death. No effect on body weight at 500 mg/kg bw in ♀. Survivors recovered lost body weight by day 7.
Oral IM-1-4	Rat, Crl:CD BR 900, 1200 or 1500 mg/kg bw	LD_{50} = 1224 mg/kg bw (♂) LD_{50} = 963 mg/kg bw (♀) LD_{50} = 1088 mg/kg bw (combined)	**Moderately toxic**, all deaths occurred within one day of dosing. Clinical signs included hypoactivity, dyspnea, gasping, salivation and convulsions. Survivors appeared normal by study day 2 and gained weight over the study period. Necropsy revealed dark red discoloration of the stomach among decedents, pale kidneys in three animals at termination and swollen mandibular lymph nodes in 1 ♀ at termination.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/d)	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Dermal IM-1-4	Rat, Crl:CD BR 2000 mg/kg bw	LD_{50} > 2000 mg/kg bw	**Low toxicity**, clinical signs observed on the day after dosing included chromodacryorrhea and crusty nose. Slight irritation was observed at the application site in all animals. Body weight was unaffected. Observations at necropsy included discolouration of the kidneys in 2 ♂, moderately reduced testicles in 1 ♂, moderately enlarged adrenal gland in 1 ♀ and uterine horns distended with fluid in 1 ♀.
ACUTE STUDIES: FORMULATION (ASSAIL BRAND 70 WP)			
Oral	Rat, Crl:CD(SD)BR 500, 1000, 1500 or 2000 mg/kg	LD_{50} = 1107 mg/kg bw (♂) LD_{50} = 944 mg/kg bw (♀) LD_{50} = 1064 mg/kg bw (combined)	**Moderately toxic**, all deaths occurred within one day of dosing except for 1 ♂ at 2000 mg/kg bw that died on study day 6. Clinical signs included laboured breathing, tremors, wobbly gait, prostration, decreased activity, decreased defecation, piloerection, urinary/fecal staining, rough coat, hair loss, hunched posture, convulsions and dilated pupils. Clinical signs persisted for 3–14 days. Body weight loss was recorded among some survivors during week 1. Necropsy observations among decedents included abnormal contents in the digestive tract, reddened mucosa in the small intestine, blackish-purple livers and mottled/reddened lungs. **WARNING POISON, skull and cross-bones enclosed in square-on-point**
Dermal	Rabbit, NZW 2000 mg/kg	LD_{50} > 2000 mg/kg	**Low toxicity**, no mortality, clinical observations limited to dark material around snout of 1 animal, days 1–3 and urine staining in 1 animal, days 1–3. Body weight unaffected, no notable observations at necropsy. Dermal irritation was observed at all test sites, persisting from 7–14 days.
Inhalation	Rat, HSD: Sprague-Dawley 2.88 mg/L	LC_{50} > 2.88 mg/L	**Low toxicity**, no mortality, clinical signs included decreased activity and piloerection on the day of exposure. All animals asymptomatic by day 2. Two ♀ lost weight during week 1. Necropsy revealed discoloured lungs in 3 ♂ and 2 ♀.

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/d)	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Eye irritation	Rabbit, NZW 0.1 mL	MAS = 2.4 MIS = 11.2 (unwashed eyes, 1 h)	**Minimally irritating**, iritis and conjunctivitis in both rinsed and non-rinsed groups at 1 h. Irritation absent in rinsed group by 48 h. Non-rinsed group irritation absent at 7 days.
Skin irritation	Rabbit, NZW 0.5 mL	MAS = 0.28 MIS = 1.17 (1 h)	**Minimally irritating**, very slight erythema in all animals with very slight edema in 1 animal at 1 h. All signs of irritation absent at 72 h.
Skin sensitization (Buehler test)	Guinea pig, Hartley-derived	Non-sensitizing	**Non-sensitizing**
ACUTE STUDIES: FORMULATION (PRISTINE BRAND RTU INSECTICIDE: 0.006% acetamiprid)			
Oral	Rat, Crl:CD(SD)BR 5000 mg/kg	LD_{50} > 5000 mg/kg	**Low toxicity**, no mortality, no clinical signs, no effect on body weight, no findings at necropsy.
Dermal	Rabbit, NZW 2000 mg/kg	LD_{50} > 2000 mg/kg	**Low toxicity**, no mortality, dermal irritation at site of application, persisting 5–14 days. No findings at necropsy.
Inhalation	Rat, HSD: Sprague-Dawley 2.11 mg/L	LC_{50} > 2.11 mg/L	**Low toxicity**, no mortality, transient laboured breathing and dark material on the snout noted on the day of dosing, slight weight loss during week 1 in 3 ♀ and in 1 female during week 2. No findings at necropsy
Eye irritation	Rabbit, NZW 0.1 mL	MAS = 0.5 MIS = 1.3 (unwashed eyes, 24 h)	**Minimally irritating**, slight conjunctivitis in 1 animal from rinsed group at 1 h, irritation absent at 24 h. Slight conjunctivitis in 3/6 and 4/6 animals in non-rinsed group at 1 and 24 h, irritation absent at 72 h.
Skin irritation	Rabbit, NZW 0.5 mL	MAS = 0.55 MIS = 1.0 (1 h)	**Slightly irritating**, very slight erythema in all animals at 1 h. All signs of irritation absent by 7 days.
Skin sensitization (Buehler test)	Guinea pig, Hartley-derived	Non-sensitizing	**Non-sensitizing**
SHORT TERM TOXICITY			
28-d dietary Note: low dose increased from 125 to 3000 ppm after 2 weeks	Beagle Dogs, 2/sex/dose at 0, 125/3000, 250, 500 or 1000 ppm (♂ = 0, 4.1/42.5, 8.4, 16.7 or 28.0 mg/kg bw/d, ♀ = 0, 4.8/46.2, 8.7, 19.1 or 35.8 mg/kg bw/d)	NOAEL = 500 ppm (16.7/19.1 mg/kg bw/d, ♂/♀) LOAEL = 1000 ppm (28.0/35.8 mg/kg bw/d, ♂/♀)	**1000 ppm (28.0/35.8 mg/kg bw/d)**: ↓ bw gain **3000 ppm (42.5/46.2 mg/kg bw/d)** marked ↓ food consumption, significant bw loss, slight ↑ absolute and relative (to brain) kidney and liver weights
21-d dermal	Rabbit, NZW 5/sex/dose at 0, 100, 500 or 1000 mg/kg bw/d	NOAEL = 1000 mg/kg bw/d	No effects on mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weights, gross or histologic pathology

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/d)	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
90-d dietary	Rat, Crj:CD (SD) 10/sex/dose at 0, 50, 100, 200, 800 or 1600 ppm (♂ = 0, 3.1, 6.0, 12.4, 50.8 or 99.9 mg/kg bw/d; ♀ = 0, 3.7, 7.2, 14.6, 56.0 or 117.1 mg/kg bw/d)	NOAEL = 200 ppm (12.4/14.6 mg/kg bw/d) LOAEL = 800 ppm (50.8/56.0 mg/kg bw/d)	**≥800 ppm (50.8/56.0 mg/kg bw/d)**: ↓bw, bw gain and food consumption; ↑ liver weight (relative to bw); ↑ centrilobular hepatocellular hypertrophy **1600 ppm (99.9/117.1 mg/kg bw/d)**: ↑ cholesterol (statistically significant in ♂ only) **Control terminal body weight:** ♂: 506.9 g; ♀: 307.6 g **Control terminal daily food consumption:** ♂: 22.0 g; ♀: 18.3 g
90-d dietary	Mouse, Crj:CD-1 (ICR) 10/sex/dose at 0, 400, 800, 1600 or 3200 ppm (♂ = 0, 53.2, 106, 211 or 430 mg/kg bw/d; ♀ = 0, 64.6, 129, 249 or 466 mg/kg bw/d)	NOAEL = 800 ppm (106/129 mg/kg bw/d) LOAEL = 1600 ppm (211/249 mg/kg bw/d)	**≥1600 ppm (211/249 mg/kg bw/d)**: ↓bw, bw gain and food consumption; ↓glucose (♂), ↓cholesterol (♀); ↓absolute and ↑(relative to body) organ weights consistent with effects on body weight **3200 ppm (430/466 mg/kg bw/d)**: mortality (2♂/2♀); weight loss; tremor in 5/10 ♀; clinical chemistry changes indicative of inanition: ↓glucose, cholesterol (♂/♀), ↑BUN, aspartate aminotransferase, alanine aminotransferase; fat depletion in the adrenal cortex; centrilobular hepatocellular hypertrophy **Control terminal body weight:** ♂: 41.22 g; ♀: 33.64 g **Control terminal daily food consumption:** ♂: 5.0 g; ♀: 4.9 g
90-d dietary	Beagle Dogs, 4/sex/dose at 0, 320, 800 or 2000 ppm (♂ = 0, 13, 32 or 58 mg/kg bw/d; ♀ = 0, 14, 32 or 64 mg/kg bw/d)	NOAEL = 320 ppm (13/14 mg/kg bw/d, ♂/♀) LOAEL = 800 ppm (32 mg/kg bw/d)	**800 ppm (32 mg/kg bw/d)**: ↓bw, bw gain and food consumption **2000 ppm (58/64 mg/kg bw/d)**: weight loss
12-month dietary	Beagle Dogs, 4/sex/dose at 0, 240, 600 or 1500 ppm (♂ = 0, 9, 20 or 55 mg/kg bw/d; ♀ = 0, 9, 21 or 61 mg/kg bw/d)	NOAEL = 600 ppm (20/21 mg/kg bw/d, ♂/♀) LOAEL = 1500 ppm (55/61 mg/kg bw/d, ♂/♀)	**1500 ppm (55/61 mg/kg bw/d)**: ↓bw, bw gain and food consumption; organ weight changes attributed to effect on bw

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/d)	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
SHORT TERM TOXICITY: METABOLITES			
90-d dietary IM-1-4	Rat, Crl:CD BR (SD) 10/sex/dose at 0, 200, 600, 1800 or 5400 ppm (♂ = 0, 12.8, 36.5, 112 or 319 mg/kg bw/d; ♀ = 0, 15.6, 44.6, 136 or 346 – 565 mg/kg bw/d)	NOAEL (♂) = 600 ppm (36.5 mg/kg bw/d) NOAEL (♀) = 1800 ppm (136 mg/kg bw/d) LOAEL (♂) = 1800 ppm (112 mg/kg bw/d) LOAEL (♀) = 5400 ppm (346–565 mg/kg bw/d)	**≥1800 ppm (112 mg/kg bw/d, ♂)**: ↑pigment in the spleen **5400 ppm (319/346–565 mg/kg bw/d)**: ↓bw, bw gain and food consumption; ↓globulin, ↑albumin–globulin ratio; organ weight changes reflective of effects on body weight; ↑pigment in the spleen (♂/♀)
90-d dietary IM-O	Rat, Crj:CD (SD), 10/sex/dose at 0, 160, 800, 4000 or 20000 ppm (♂ = 0, 9.9, 48.9, 250 or 1247 mg/kg bw/d; ♀ = 0, 11.1, 55.9, 276 or 1174 mg/kg bw/d)	NOAEL (♂) = 800 ppm (48.9 mg/kg bw/d) NOAEL (♀) = 4000 ppm (276 mg/kg bw/d) LOAEL (♂) = 4000 ppm (250 mg/kg bw/d) LOAEL (♀) = 20000 ppm (1174 mg/kg bw/d)	**≥4000 ppm (250 mg/kg bw/d, ♂)**: ↑ eosinophilic intranuclear inclusions in proximal tubular epithelium of the kidney **20000 ppm (1247/1174 mg/kg bw/d)**: ↓bw, bw gain, food consumption and food efficiency; ↑ incidence of eosinophilic intranuclear inclusions in proximal tubular epithelium of the kidney in ♀ and ↑ incidence and severity of same lesion in ♂.
CHRONIC TOXICITY AND ONCOGENICITY			
78-week dietary	Mouse, Crl:CD-1 (ICR) BR 50/sex/dose, plus 10/sex/dose for interim sacrifice at 52 weeks at 0, 130, 400 or 1200 ppm (♂ = 0, 20.3, 65.6 or 186 mg/kg bw/d; ♀ = 0, 25.2, 75.9 or 215 mg/kg bw/d)	NOAEL = 400 ppm (65.6/75.9 mg/kg bw/d) LOAEL = 1200 ppm (186/215 mg/kg bw/d)	**1200 ppm (186/215 mg/kg bw/d)**: ↓bw, bw gain, food consumption and food efficiency; organ weight changes consistent with effect on body weight; centrilobular hepatocellular hypertrophy **No evidence of oncogenicity**
2-year dietary	Rat, Crl:CD BR 60/sex/dose at 0, 160, 400 or 1000 ppm 10/sex/dose sacrificed at 12 months for interim evaluations (♂ = 0, 7.1, 17.5 or 46.4 mg/kg bw/d; ♀ = 0, 8.8, 22.6 or 60.0 mg/kg bw/d)	NOAEL = 160 ppm (7.1/8.8 mg/kg bw/d) LOAEL = 400 ppm (17.5/22.6 mg/kg bw/d)	**≥400 ppm (17.5/22.6 mg/kg bw/d)**: ↓bw, bw gain (♀); ↑incidence of hepatocellular hypertrophy and hepatocellular vacuolation (♂) **1000 ppm (46.4/60.0 mg/kg bw/d)**: clinical signs (♂) during second year of study: ↑rales, laboured breathing, hunched posture; ↓bw, bw gain and food consumption (♂/♀); organ weight changes consistent with reduced body weights; ↑incidence of microconcretions in renal papillae (♂); ↑incidence of mammary hyperplasia (trace) **No definitive evidence of oncogenicity**

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/d)	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
REPRODUCTION AND DEVELOPMENTAL TOXICITY			
Multi-generation reproduction	Rat, Crl:CD BR (IGS) 26/sex/dose at 0, 100, 280 or 800 ppm (♂ = 0, 6.5, 17.9 or 51.0 mg/kg bw/d; ♀ = 0, 7.6, 21.7 or 60.1 mg/kg bw/d)	NOAEL (parental) = 280 ppm (17.9/21.7 mg/kg bw/d) LOAEL (parental) = 800 ppm (51.0/60.1 mg/kg bw/d) NOAEL (offspring) = 280 ppm (17.9/21.7 mg/kg bw/d) LOAEL (offspring) = 800 ppm (51.0/60.1 mg/kg bw/d) NOAEL (reproductive) = 280 ppm (17.9/21.7 mg/kg bw/d) LOAEL (reproductive) = 800 ppm (51.0/60.1 mg/kg bw/d)	**800 ppm (51.0/60.1 mg/kg bw/d)**: ↓bw, bw gain and food consumption, ♂/♀, both generations; ↓litter size, viability index and weaning index in F_2 pups; ↓litter weights and individual pup weights, both generations; delays in age to attain vaginal opening and preputial separation; delayed eye opening and pinna unfolding in F_2 pups **Qualitative evidence of sensitivity of offspring** (offspring effects more severe than parental effects at same dose level)
Developmental toxicity	Rat, Crj:CD(SD) 24 pregnant ♀/dose at 0, 5, 16 or 50 mg/kg bw/d from day 6 to 15 of gestation	NOAEL (maternal) = 16 mg/kg bw/d LOAEL (maternal) = 50 mg/kg bw/d NOAEL (developmental) = 16 mg/kg bw/d LOAEL (developmental) = 50 mg/kg bw/d	**50 mg/kg bw/d**: ↓maternal bw, bw gain and food consumption, ↑absolute and relative (to body) liver weights ↑incidence of skeletal variation shortening of 13th rib **No evidence of teratogenicity**
Developmental toxicity	Rabbit, Kbs:NZW 17 pregnant ♀/dose at 0, 7.5, 15 or 30 mg/kg bw/d from day 6 to 18 of gestation	NOAEL (maternal) = 15 mg/kg bw/d LOAEL (maternal) = 30 mg/kg bw/d NOAEL (developmental) = 30 mg/kg bw/d	**30 mg/kg bw/d**: maternal bw loss gestation days (GD) 6–10, ↓food consumption GD 6–8 No treatment related changes in any developmental parameters **No evidence of teratogenicity**
NEUROTOXICITY			
Acute neurotoxicity	Rat, Crl CD BR, 10/sex/dose at 0, 10, 30 or 100 mg/kg bw	NOAEL = 10 mg/kg bw LOAEL = 30 mg/kg bw	**30 mg/kg bw/d**: ↓Motor activity (♂); slight decrease in duration of movements persisted until day 14 **100 mg/kg bw/d**: ↓body temperature, ↓motor activity, FOB findings day 0: ♂: tremors, difficulty handling, walking on toes, dilated pupils, cold to touch, ↓hind limb grip strength and hind limb foot splay; ♀: tremors, chewing, cold to touch and dilated pupils, ↓hind limb foot splay, abnormal gaits and (or) posture

STUDY	SPECIES/STRAIN AND DOSES	NOAEL and LOAEL (mg/kg bw/d)	TARGET ORGAN/ SIGNIFICANT EFFECTS/ COMMENTS
Subchronic neurotoxicity	Rat, Crl CD BR, 10/sex/dose at 0, 100, 200, 800 or 1600 ppm (♂ = 0, 7.4, 14.8, 59.7 or 118 mg/kg bw/d; ♀ = 0, 8.5, 16.3, 67.6 or 134 mg/kg bw/d)	NOAEL = 200 ppm (14.8/16.3 mg/kg bw/d) LOAEL = 800 (59.7/67.6 mg/kg bw/d)	**800 ppm (59.7/67.6 mg/kg bw/d):** ↓bw, bw gain, food consumption and food efficiency **No evidence of neuropathology**
GENOTOXICITY			
STUDY	**SPECIES AND STRAIN OR CELL TYPE AND CONCENTRATIONS OR DOSES EMPLOYED**		**RESULTS**
Gene mutations in bacteria	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537; *E. coli* WP2uvrA 313–5000 µg/plate; with and without activation		Negative
Gene mutations in mammalian cells in vitro	Chinese hamster ovary cells (HGPRT locus) 500–4000 µg/mL without activation 250–3500 µg/mL with activation		Negative
Unscheduled DNA synthesis (in vivo/in vitro)	Primary rat hepatocytes, isolated from male HSD rats 75, 150 or 300 mg/kg (single oral dose; primary cultures scored for UDS 2–4 and 12–16 h after dose administration)		Unacceptable: too few animals, HDT not maximal
Chromosome aberrations in vitro	Chinese hamster ovary cells 175, 350 or 700 µg/mL without activation 337.5, 675 or 1350 µg/mL with activation		Slight positive response –S9[a] Dose-dependent positive response +S9 Clastogenic under conditions tested
Unscheduled DNA synthesis in vitro	Primary rat hepatocytes, isolated from ♂ Fischer 344 rats 10–500 µg/mL		Negative
Micronucleus assay (in vivo)	♂ and ♀ CD-1 (ICR) mice 0, 20, 40 or 80 mg/kg (single oral dose; bone marrow harvested 24, 48 and 72 h post-dosing)		Negative
Chromosome aberrations in vivo	♂ and ♀ Crl:CD(SD) rats 250 mg/kg bw (MTD); single oral dose, sacrificed at 6, 24 or 48 h and bone marrow harvested		Negative
GENOTOXICITY: METABOLITES			
Gene mutation in bacteria IM-1-4	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537; *E. coli* WP2uvrA 313–5000 µg/plate; with and without activation		Negative
Gene mutations in mammalian cells in vitro IM-1-4	Chinese hamster ovary cells (HGPRT locus) 250–3500 µg/mL with activation		Negative
Micronucleus assay (in vivo) IM-1-4	Male and female Crl:CD-1 (ICR) mice (6/sex) 0, 175, 350 or 700 mg/kg (single oral dose; bone marrow harvested 24, 48 and 72 h post-dosing)		Negative
Gene mutation in bacteria IM-1-2	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537; *E. coli* WP2uvrA 313–5000 µg/plate; with and without activation		Negative

STUDY	SPECIES AND STRAIN OR CELL TYPE AND CONCENTRATIONS OR DOSES EMPLOYED	RESULTS
Gene mutation in bacteria IM-2-1	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537; *E. coli* WP2uvrA 313–5000 µg/plate; with and without activation	Negative
Gene mutation in bacteria IM-O	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537; *E. coli* WP2uvrA 313–5000 µg/plate; with and without activation	Negative
Gene mutation in bacteria IC-O	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537; *E. coli* WP2uvrA 313–5000 µg/plate; with and without activation	Negative
Compound-induced mortality: Mouse subchronic toxicity study: 2 ♂ and 2 ♀ at 3200 ppm (430.4/466.3 mg/kg bw/d)		
Recommended ARfD: 0.1 mg/kg bw/d, based on NOAEL of 10 mg/kg bw/d from rat acute neurotoxicity study, using UF/SF of 100		
Recommended ADI: 0.023 mg/kg bw/d, based on NOAEL of 7.1 mg/kg bw/d from rat chronic toxicity and oncogenicity study, using UF/SF of 300		

[a] S9, exogenous metabolic activation system

Appendix IV Residues

Integrated food residue chemistry summary table

PARAMETER		PERTINENT INFORMATION				
CHEMICAL		Acetamiprid				
Crop	**Formulation and type**	**Method and timing**	**Rate (g a.i./ha)**	**Number per season**	**Maximum rate (g a.i./ha)**	**PHI (d)**
Leafy vegetables, crop group 4: amaranth leafy, arugula, cardoon, celery, celery (Chinese), celtuce, chervil, chrysanthemum (edible-leaved), chrysanthemum (garland), corn salad, cress (garden), cress (upland), dandelion leaves, dock, endive, fennel (Florence), lettuce (head and leaf), orach, parsley leaves, purslane (garden), purslane (winter), radicchio, rhubarb, spinach, spinach (New Zealand), spinach (vine), Swiss chard	**Assail Brand 70 WP**	Broadcast foliar ground or aerial	60	5	300	7
Cole crops, crop group 5: broccoli, broccoli (Chinese), broccoli raab, Brussels sprouts, cabbage, cabbage (Chinese, bok choy), cabbage (Chinese, napa), cabbage (Chinese mustard, gai choy), cauliflower, cavalo broccolo, collards, citrus (dried pulp), kale, kohlrabi, mizuna, mustard greens, mustard spinach, rape greens	**Assail Brand 70 WP**	Broadcast foliar ground or aerial	84	5	420	7

Fruiting vegetables, crop group 8: tomato, peppers: bell, chili, cooking, pimento, and sweet, eggplant, ground cherry	**Assail Brand 70 WP**	Broadcast foliar ground or aerial	84	5	420	7
Pome fruit, crop group 11: apple, crabapple, loquat, mayhaw, pear, pear (oriental), quince	**Assail Brand 70 WP**	Broadcast foliar ground or aerial	168	4	672	7
Grapes	**Assail Brand 70 WP**	Broadcast foliar ground or aerial	56	2	112	7
LABEL RESTRICTIONS		none				
PHYSICOCHEMICAL PROPERTIES		**Value**				
Water solubility at 25°C		pH / Solubility (mg/L) Distilled H_2O — 4.25×10^3 5.0 — 3.48×10^3 7.0 — 2.95×10^3 9.0 — 3.96×10^{-3} Buffer solutions are used at pH 5, 7 and 9				
Solvent solubility at 20°C		Solvent / g/100 mL Benzene — 2.44 Xylene — 4.01 *N*-hexane — 6.54 ppm CS_2 — 507 ppm Acetone, methanol, ethanol, DCM, chloroform, ACN, tetrahydrofuran, each at >20 g/100 mL				
K_{ow} at 25°C		$K_{ow} = 6.27$ $\log K_{ow} = 0.80$				
p*K*a		p*K*a = 0.7 at 25°C				
Vapour pressure at 25°C		$<1 \times 10^{-6}$ Pa (1×10^{-8} mm Hg)				
NATURE OF THE RESIDUE: ANIMALS		Leghorn laying hens and lactating goats				
Radiolabelling positions		Experiments were carried out with [Pyridine 2,6-^{14}C]acetamiprid (technical grade active ingredient (TGAI); >99% a.i.).				
Proposed metabolic pathway		The metabolism of acetamiprid in rat, ruminants and poultry is similar. Excretion was rapid and occurred mostly through urine, but also in feces. The major pathway of metabolism involves involves the demethylation of the parent to yeild IM-2-1followed by sequential hydrolysis of the cyano-methylacetamidine moiety to yeild either IM-2-4 via IM-2-3 or IM-2-5 via IM-2-2. In addition, the parent and its major metabolite IM-2-1 can be				

ROC	degraded directly to IC-O by side chain cleavage in both animal species. Within goat muscle, IM-2-1-imide is seen as a predominant metabolite. For enforcement purposes, the ROC for livestock commodities should be acetamiprid plus its IM-2-1 metabolite namely: the sum of (*E*)-N^1-[(6-chloro-3-pyridyl)-methyl]-N^2-cyano-N^1-methyl acetamidine and N^1-[(6-chloro-3-pyridyl) methyl]-N^2-cyano-acetamidine. For purposes of risk assessment, the residues of concern in livestock tissue except ruminant muscle are acetamiprid plus its IM-2-1 metabolite. In ruminant muscle, the residues of concern for risk assessment are acetamiprid plus IM-2-1 plus IM-2-1-amide.
Comparison of metabolic profiles	The metabolic profile of acetamiprid was similar in goat, hen and rat. The overall comparison of the metabolites identified demonstrated that the metabolism of acetamiprid in all three species proceeded via the same major metabolic pathways, therefore, a swine metabolism study was not required.
NATURE OF THE RESIDUE: PLANTS	Studies in apples, carrots, cabbage, cotton and eggplant as well as rotational crops.
Radiolabelling positions	Experiments were carried out with [Pyridine 2,6-^{14}C]acetamiprid (TGAI; >99% a.i.).
Proposed metabolic pathway	The qualitative nature of acetamiprid in target crops is adequately understood. Though quantitative differences were observed between the different metabolism studies, these differences do not preclude the PMRA from concluding that the nature of the residues in three diverse crops is understood. Metabolism of the parent in plants can occur by hydrolysis to yield IM-1-2 or by demethylation to yield IM-2-1. In carrots, the primary pathway appears to be by hydrolysis whereas in other crops examined, the dominant pathway is by demethylation. The further degradation of IM-1-2 and IM-2-1 yields the same end products namely, IC-O and IM-O-Glc. In all plant species used, parent can also be degraded directly to IC-O vis side chain cleavage.
ROC	The ROC is defined as the parent acetamipand namely: (*E*)-N^1-[(6-chloro-3-pyridyl)-methyl]-N^2-cyano-N^1-methyl acetamidine.
Novel plant metabolites	None of toxicological concerns identified
Residue analytical method	Plant and animal matrices
Method ID	The petitioner is proposing two methods for the analysis of acetamiprid in a variety of plant commodities: Method 1 is a GC–ECD method for analysis of fruits (non-citrus) and vegetables and Method 2 is an HPLC–UV method for analysis of citrus commodities. The petitioner is also proposing two methods (HPLC–UV) for the analysis of acetamiprid in animal commodities. For the analysis of ruminant commodities, the analytical method is references as Method AR 149-97, and in poultry commodities the analytical method is designated as Method AR 151-97.
Analytes	In plants: Acetamiprid In animals: Acetamiprid plus IM-2-1

Instrument or detector	For plants: Method 1 Non-citrus The chromatography and detection was carried out on a Hewlett-Packard gas chromatography system equipped with an ECD (Model 5890 Series). For plants: Method 2 Citrus The chromatography was carried out by HPLC (instrument unspecified) with UV detection at 254 nm (detector make unspecified). For animals: Ruminant An HPLC method carried out on a Merck Hitachi instruments; HPLC (model L-6200) autosamples (model AS-4000) and detector (L-4000). For animals: Poultry An HPLC method carried out on a Merck Hitachi instruments; HPLC (model L-6200) autosamples (model AS-4000) and detector (L-4000).
Instrument parameters	For plants: Method 1, Non-citrus GC–ECD Temperatures Injector: 300°C Column: 150°C initially, ramp to 260°C at 40°C/min, hold for 8 min, ramp again at 40°C/min to 280°C hold for 3 min Detector: ECD at 300°C Injection volume: 1–2 µL depending on instrument sensitivity Flow rate: Carrier gas He at 10.0 mL/min For plants: Method 2 Citrus HPLC–UV Temperatures 40°C (column only, injector at room temperature) Detector(s): in UV mode: 254 nm Injection volume: 100 µL Gradient: Solvent A = 95:5 water:THF Solvent B = 95:5 ACN: THF Time (min) / Solvent A / Solvent B 0 / 85 / 15 12 / 65 / 35 13 / 65 / 35 14 / 10 / 90 18 / 10 / 90 19 / 85 / 15 Flow rate: 1 mL/min Run time: 23 min (including re-equilibation time) **For Both Ruminant and Poultry Methods HPLC-UV** Temperatures: ambient Detector(s): UV at 254 nm Injection volume: 100µL Gradient: isocratic elution with a 75:20:5 water:ACN:THF LC–MS–MS for confirmatory analysis Temperatures: ambient Detector(s): Detection of parent at m/z 223 (M^+) for parent and m/z

	209 (M*) for IM-2-1 Injection volume: 30 µL Gradient: A= 0.5% (v/v) acetic acid in water B= ACN Time (min) / Solvent A / Solvent B 0 / 90 / 10 15 / 20 / 80 20 / 20 / 80 20.1 / 90 / 10 30 / 90 / 10 Flow rate 1.0 mL/min Run time: 30 min
Column	For plant matrices, Method 1 Non-citrus GC–ECD J and W DB-1701 15 m × 0.53 mm, 1.0 µm film thickness For plant matrices, Method 2 Citrus HPLC–UV Zorbax SB-Phenyl 250 × 4.6 mm, 5.0 µm For animal matrices HPLC–UV Zorbax SB-Phenyl 250 × 4.6 mm, 5.0 µm For animal matrices confirmatory LC–MS–MS Merck LiChrospher C8 column, particle size unspecified
Standardization method	By comparative real-time analysis or by spectroscopic methodology (UV)
Stability of primary and (or) secondary standard solutions	Established for the length of the various experiments
Retention times	For plant matrices, Method 1 Non-citrus GC–ECD Parent calculated 7.7 min For plant matrices, Method 2 Citrus HPLC–UV Parent 10.1 min For animal matrices HPLC–UV Ruminant: parent 10.75, IM-2-1, 8.5 Poultry: parent 11.25, IM-2-1, 8.25
Limit of detection (LOD)	For plant matrices, Method 1 Non-citrus GC–ECD LOD not stated, instrument LOD was 0.0005 ppm For plant matrices, Method 2 Citrus HPLC–UV LOD not stated, instrument LOD was 0.005 ppm For animal matrices, HPLC–UV Ruminant: Calculated LOD for parent = 0.003 ppm and IM-2-1 = 0.006 ppm Poultry: same
LOQ	For plant matrices, Method 1 Non-citrus GC–ECD 0.01 ppm For plant matrices, Method 2 Citrus HPLC–UV 0.05 ppm For animal matrices HPLC–UV Ruminant: parent and IM-2-1 LOQ = 0.05 ppm for liver and kidneys and 0.01 ppm for all other substrates Poultry: parent and IM-2-1 LOQ 0.05 ppm for liver and 0.01 ppm for all other substrates

Repeatability and precision	The mean RSDs for various spiking levels for each anolytes in plant an animal matrices were good. The values obtained are indicative of the method having good repeatability. In most cases, the RSDs measured with respect to recoveries following spiking at the LOQ were less than 20% for all matrices. The values obtained are indicative of the method having good repeatability.
Reproducibility	A method ILV was conducted to verify the reliability and reproducibility of all methods in in various plant and animal matrices. In general, the method ILV trials for the determination of the analytes were successful in all matrices with the exception of muscle.
Linearity	Correlation coefficient was greater than 0.998 in all experiments.
Specificity	The control sample chromatograms generally had no peaks above the chromatographic background and the spiked sample chromatograms contained only the analyte peak. The peak was well defined and symmetrical. There appeared to be no carryover to the following chromatograms.
Multiresidue method	The petitioner submitted data concerning the recovery of residues of acetamiprid using FDA multiresidue method protocols (PAM Vol. I). Protocol A: The test substance is not an *N*-methylcarbamate structure. Protocol C: Gas chromatographic screenings were conducted with acetamiprid dissolved in acetone. The results from gas chromatographic investigations are reported as a ratio of peak retention time in minutes relative to that of the marker chemical, chlorpyrifos. Since the test substance was chromatographic, testing under Protocols D, E, and F was conducted. Protocol D: Recovery testing through the complete method without the Florisil cleanup for nonfatty matrices was conducted using a DB-1 column with nitrogen phosphorus detection. Oranges were selected as the non-fatty food sample. Duplicate orange samples were fortified with acetamiprid at 0.05 and 0.25 ppm. Recoveries ranged from 0.0% to 41.2% in four samples; average recovery of acetamiprid was 21.6% ± 20.7%. Protocol E: Acetamiprid was analyzed for recoveries from the Florisil column using the methodology of Protocol E 303/Protocol F 304 C1 and C2. Duplicate Florisil columns were loaded with the test substance and eluted per the respective methods. For C1, recoveries ranged from 0.0% to 20.4%. For C2, recoveries ranged from 0.0% to 11.3%. Because recoveries through both elution systems were <30%, further work was discontinued. Protocol F: Recovery of acetamiprid was <30% using Protocol E; thus an evaluation through Protocol F was not conducted.
Storage stability data	The stability of acetamiprid during short-term storage at ambient temperatures and during extended storage at freezer temperatures was evaluated. In the ambient temperature storage stability study, samples of cottonseed, cotton gin trash, cottonseed oil, whole grapes, grape juice, raisins, whole oranges, whole tomatoes, and tomato paste spiked with acetamiprid at 0.10 and 0.25 ppm were stored at ambient temperatures for a duration of 7 days (15 days for raisins). Under these conditions, residues of acetamiprid were stable in all commodities. In the freezer storage stability study, samples of whole apple, apple juice,

	wet apple pomace, cabbage, cottonseed, cotton gin trash, cottonseed hulls, meal, and oil, cucumber, head lettuce, whole orange, and orange juice, oil, and dried pulp spiked with acetamiprid at 0.10 and 0.50 ppm were stored frozen (–35 to 6°C) for duration of 12 months (~15 months for head lettuce). Under these conditions, residues of acetamiprid were stable in all commodities. The maximum storage intervals for the various animal fractions were less than one month from sample collection (–20 to 4°C). Given the short period of time, supporting storage stability data are not required.
CROP FIELD TRIALS	**Leafy Vegetable Crop Group** Multiple residue trials were carried out in the representative crops of crop group 4: celery, lettuce and spinach. All of the trials submitted in support of an MRL on this crop group were carried out at 1.4× the maximum sustainable rate. The results from the U.S. trials showed that in celery, the MRL observed was 0.780 ppm; head lettuce, the MRLs were 0.743 ppm in or on head lettuce with wrapper leaves and 0.294 ppm in head lettuce without wrapper leaves; in leaf lettuce, the MRL observed was 1.07 ppm; and in spinach, the MRL observed was 2.58 ppm. From the trials carried out in Canadian zones, the residues were in head and leaf lettuce, 0.18 ppm (vs. 0.743 ppm in the U.S.) and in spinach, 0.23 ppm (vs. 2.58 ppm in U.S.). No residue trials in celery were carried out in zones applicable to Canada. For the leafy vegetables group, the number and location of the trials submitted does not satisfy the requirements set out in the Canadian Residue Chemistry Guidelines. The registrant is deficient in a total of six trials in the various representative crops. As the residues in lettuce and spinach trials were 6–11× lower in Canada than in the U.S. lettuce and spinach trials and due to the high quality of the data submitted as well as the residue profile observed, the PMRA has decided to grant the registrant partial relief from the full requirements of Dir98-02. Consequently, a crop group MRL of 3.0 ppm will be recommended conditional on the registrant providing one additional trial for lettuce from zone 5B and two additional trial carried out in zone 5B on celery.
	Brassica (Cole) Leafy Vegetables Group Multiple residue trials were carried out in the representative crops of crop group 5: broccoli, cabbage and mustard greens. All of the trials submitted in support of an MRL on this crop group were carried out at 1× the maximum sustainable rate. The results from the U.S. trials indicate that in broccoli the MRL was 0.25 ppm, in cabbage the MRLs were 0.50 ppm in or on cabbage with wrapper leaves and 0.05 ppm in or on cabbage without wrapper leaves and in mustard greens the MRL was 1.1 ppm. The results from trials conducted in zones applicable to Canada have shown that the MRLs observed are lower in zones applicable to Canada. For broccoli, the highest residue level observed was 0.1ppm (vs. 0.25 ppm in the U.S.), for cabbage the residue were 0.0.11 and 0.027 ppm for cabbage with and with out wrapper leaves (vs. 0.5 and 0.05 ppm in the U.S. for cabbage with and without wrapper leaved). No residue trials in mustard greens were carried out in zones applicable to Canada. The number and location of the trials submitted does not satisfy the requirements set out in the Canadian Residue Chemistry Guidelines. The registrant is deficient in a total of six trials in the various representative crops. We note that the MRLs reported for acetamiprid residues in the

	Canadian broccoli and cabbage trials were generally lower than the MRLs in the U.S. broccoli and cabbage trials. Due to the high quality of the data submitted, the PMRA has decided to grant the registrant partial relief from the full requirements of Dir98-02. Consequently, the PMRA will only require one additional trial for broccoli and cabbage carried out in zone 5B as a condition of registration. Based on the available data for broccoli, cabbage, and mustard greens, a crop group MRL of 1.2 ppm, would be adequate to cover residues of acetamiprid in the brassica (cole) leafy vegetables group, crop group 5.
	Fruiting Vegetables (Except Cucurbits) Group Multiple residue trials were carried out in the representative crops of crop group 8: tomato and peppers. In addition, the registrant has submitted residue trials in eggplants in support of the proposed crop group MRL. All of these trials were carried out in multiple U.S. zones. Only two trials were carried out in zones applicable to Canada. All of the trials submitted in support of an MRL on this crop group were carried out at 1× the maximum sustainable rate. The results from the U.S. supervised crop field trials in tomato have shown that the MRL was 0.11 ppm. In bell and non-bell pepper the MRLs were 0.09 ppm in or on bell peppers and 0.16 ppm, respectively. Results from the trials in eggplant trials showed that the MRL was 0.05 ppm. The number and location of the trials submitted does not satisfy the requirements set out in the Dir98-02, Section 9. Only 2 of the required 17 trials can be considered in a domestic registration. As there are few trials in common zones, the PMRA cannot consider a domestic registration on the whole crop group based on the trials submitted. A temporary domestic registration on tomatoes as a single commodity can, however, be supported pending the submission of four additional trials from zone 5 and one additional trial carried in zone 5B. The PMRA will recommend an MRL in the fruiting vegetables to cover the residues of acetamiprid resulting from the domestic registration on tomatoes and for fruiting vegetables crops imported from the U.S. Based on the available data for eggplants, peppers, and tomatoes, a crop group MRL of 0.2 ppm is recommended to match the crop group tolerance proposed by the U.S. EPA to cover residues of acetamiprid in the fruiting vegetables (except cucurbits) group, crop group 8.
	Citrus Fruits Group The results from the supervised crop field trials in citrus have shown that the MRLs observed in the representative crops were oranges, 0.29 ppm, grapefruit, 0.27 ppm and lemon, 0.39 ppm. Based on the available data for grapefruit, lemons and oranges, a crop group MRL of 0.5 ppm would be adequate to cover residues of acetamiprid in the citrus fruits group, crop group 10.
	Pome Fruit Crop Group Multiple residue trials were carried out in the representative crops of crop group 11: apples and pears. All of the trials submitted in support of an MRL on this crop group were carried out at 1× the maximum sustainable rate. The results from U.S. trials in apples have shown that the MRL was 0.64 ppm. In pears the MRLs was 0.36 ppm. The results from trials conducted in zones applicable to Canada carried out at the same application

	rate as those in unique U.S. zones have shown that the MRLs observed are lower in zones applicable to Canada for apples (0.3 vs. 0.64 ppm). In contrast, the residues observed in pears were higher in Canadian zones than the those observed in U.S. zones (0.71 vs. 0.36 ppm). The number and location of the trials submitted does not satisfy the requirements set out in Dir98-02. The registrant is missing a total of three trials. Due to the high quality of the data submitted, the PMRA has decided to grant the registrant partial relief from the full requirements of Dir98-02. Consequently, the PMRA will only require one additional trial for apples an zone 5B and one additional trial carried out in zone 1A on pears as a condition of the Canadian registration. An MRL of 1.0 ppm is needed to cover the residue in this crop group.
	Grapes The results from the grape supervised crop field trials carried out in U.S. zones have shown that the MRL in grapes was 0.14 ppm. The MRL observed in trials carried out in zones applicable to Canada was 0.084 ppm. The number and location of the trials submitted does not satisfy the requirements set out in the Canadian Residue Chemistry Guidelines. The registrant is missing a total of three trials domestically. Due to the high quality of the data submitted, the PMRA has decided to grant the registrant partial relief from the full requirements of Dir98-02. Consequently, the PMRA will only require two additional trial carried out in zone 5 as a condition of registration. Based on the available U.S. and Canadian data, an MRL of 0.2 ppm would be adequate to cover residues of acetamiprid in or on grapes.
	Cotton The results from the supervised crop field trials in cottonseed and cotton gin trash have shown that the MRLs were 0.50 ppm for undelinted cottonseed and 19.2 ppm for cotton gin trash. Based on the available data for cotton, The U.S. will set tolerances of 0.6 ppm for cottonseed and 20 ppm for cotton gin trash. There are currently no Codex MRLs established for acetamiprid; Mexican MRLs have been established for cottonseed at 0.010 ppm and potato at 0.5 ppm. Upon further investigation, the difference between the tolerance recommended by the EPA and the allowable levels in Mexico are related to the formulation and the timing of application. Canada will recommend an MRL of 0.6 ppm to cover potential residues of acetamiprid in cottonseed.
Residue decline	Residue decline studies with acetamiprid have been conducted with representative crops including cotton, head lettuce, oranges, pears and pepper. These studies indicate that generally, residues of acetamiprid did not increase with increasing post-treatment intervals following the last application.
Processed food or feed	Processing studies were carried out in tomato, oranges, apple, grape and cotton. In tomato, concentration factors of 1.4 and 3.0× for tomato puree and paste, were determined. The HAFT residue from tomato trials reflecting the maximum proposed use pattern is 0.10 ppm. Based on the HAFT and the concentration factors, the maximum expected acetamiprid residues in

	tomato puree and paste would be 0.14 and 0.3 ppm, respectively. The expected residues in tomato puree are less than the proposed MRL for tomato RAC (0.2 ppm); therefore, a separate MRL does not need to be established for tomato puree. However, an MRL needs to be established to cover residues of acetamiprid in tomato paste. An MRL of 0.4 ppm for residues of acetamiprid in tomato paste is recommended. In oranges, concentration factors of <0.16, 2.8 and <0.16× for juice, dried pulp and citrus oil, respectively, were experimentally derived. The HAFT residue from citrus trials reflecting the maximum proposed use pattern is 0.34 ppm (in lemons). Based on the HAFT and the concentration factors, the maximum expected acetamiprid residues in juice, dried pulp, and oil would be <0.06, 1.0 and <0.06 ppm, respectively. The expected residues in juice and citrus oil are less than the proposed MRLs for citrus RAC (0.5 ppm); therefore, MRLs do not need to be established for citrus juice or oil. However, an MRL needs to be established to cover residues of acetamiprid in citrus dried pulp. An MRL of 1.2 ppm for residues of acetamiprid in citrus dry pulp is proposed. In apples, the registrant has submitted data that illustrated that residues of acetamiprid has concentration factors of 0.88 and 1.4× for apple juice and wet apple pomace, respectively. The HAFT residue from apple trials reflecting the maximum proposed use pattern is 0.59 ppm. Based on the HAFT and the concentration factor, the maximum expected acetamiprid residues in wet apple pomace would be 0.83 ppm, respectively. Because residues did not concentrate in apple juice, no MRL for acetamiprid residues in apple juice is required. In grapes the maximum theoretical concentration factors are 1.2× for grape juice and 4.7× for raisins. Since the observed factor for juice of 1.5× exceeds the maximum theoretical factor of 1.2×, the theoretical factor will be used to calculate the expected residues in grape juice. The HAFT residue from grape trials reflecting the maximum proposed use pattern is 0.13 ppm. Based on the HAFT and the concentration factors (experimental for raisins and theoretical for juice), the maximum expected acetamiprid residues in grape juice and raisins would be 0.16 ppm and 0.12 ppm, respectively. The expected residues in grape juice and raisins are less than the proposed MRL for grape RAC (0.2 ppm); therefore, MRLs do not need to be established for grape juice and raisins. In the processed food study on cotton, registrant was able to determine average concentration or reduction factors of 0.38×, 0.80× and <0.04× for meal, hulls and refined oil, respectively. Because residues of acetamiprid did not concentrate in cottonseed processed commodities, no MRLs for cotton seed refined oil need to be established.
Dairy cattle feeding	Acetamiprid was administered orally to nine Holstein dairy cows for 28 days. The dosages were equivalent to 6 ppm (1.3×), 18 ppm (4.0×) and 60 ppm (13×) in the diet. Potential ruminant feed items associated with this petition are wet apple pomace, canola meal, dried citrus pulp, undelinted cottonseed, cotton gin byproducts, cottonseed meal and hulls. Based on the supervised field trials, cotton gin byproducts would be expected to contribute the highest acetamiprid residues to cattle dietary burden. Using a diet consisting of cotton gin byproducts and cottonseed meal, the maximum theoretical dietary burden of acetamiprid to dairy cattle is 4.545 ppm. These feed RACs represent 35% of the total diet for dairy and beef cattle; a diet consisting of other ruminant feed items associated with this petition, in addition to cotton gin byproducts and cottonseed meal, is not considered to

	be realistic. As cotton feed items are predominantly a U.S. feed item the anticipated dietary burden to cattle in Canada is considerably less. The expected residues of acetamiprid in milk, meat and meat byproducts resulting from the feeding of crops treated with acetamiprid under the conditions proposed in this petition are <0.01–0.018 in milk, <0.01 in fat and muscle and <0.05 ppm in kidney and liver. The metabolism studies indicated that the residues of concern in ruminant commodities are the combined residues of acetamiprid and IM-2-1. MRLs of 0.1 ppm for meat, fat and milk and 0.3 ppm for meat byproducts are recommended. The lactating goat metabolism study also indicated that IM-2-1 serves as a marker compound for IM-2-1-amide. Based on data from the lactating goat metabolism study, IM-2-1-amide occurs at not more than 10 times the level of IM-2-1 in ruminant muscle tissues. Though IM-2-1 is not included in the ROC for monitoring purposes, it presence must be accounted for in the DRA.
Poultry feeding	In the poultry feeding study acetamiprid was administered orally to 30 White Leghorn laying hens for 28 d. The dosages were equivalent to 1.2 ppm (9.8×), 3.6 ppm (30×) and 12 ppm (98×) in the diet. Potential poultry feed items associated with this petition are canola meal and cottonseed meal. Using a diet consisting of canola meal and cottonseed meal, the MTDB of acetamiprid to poultry is 0.122 ppm. These feed RACs represent 35% of the total diet for poultry. As cotton feed items are primarily of U.S. origin, the calculated MTDB is an over estimate for Canadian poultry. The expected residues of acetamiprid in eggs, meat, and meat byproducts resulting from the feeding of crops treated with acetamiprid under the conditions proposed in this petition are <0.01 ppm in eggs, fat and muscle and <0.05 ppm in liver. Expected residues of the metabolite IM-2-1 are 0.01 ppm in liver, 0.003 ppm in eggs, and <0.01 ppm in fat and muscle. The residues of concern in livestock and poultry are acetamiprid and IM-2-1. MRLs at the LOQ for poultry commodities (0.01 ppm for muscle, fat and eggs and 0.05 ppm for organ meats and meat byproducts) will be proposed.
Confined rotational crops	The PMRA reached the following conclusions regarding the confined rotation studies. The major metabolite in rotational crops, IM-1-4, was also observed, directly or indirectly, in cotton, apple, carrot and cabbage (not eggplant) metabolism studies. This metabolite was the primary soil metabolite. In addition, metabolite IC-O and its glycoform (IC-O-Glc) were also observed in four of the metabolism studies carried out on primary crops (apple, carrot, cabbage and eggplant, not cotton).
Field accumulation: rotational crops	The confined crop rotation studies indicated that no field rotational crop studies are needed at this time.
Proposed MRLs	Vegetable, leafy, except brassica, group, crop group 4 — 3.0 Vegetable, brassica, leafy, group, crop group 5 — 1.2 Fruit, pome, group, crop group 11 — 0.7 Grape (tomatoes covered under import MRLs) — 0.2 Cattle, meat; hog, meat; horse, meat; goat, meat; sheep, meat — 0.1 Cattle, fat; hog, fat; horse, fat; goat, fat; sheep, fat — 0.1 Cattle, meat byproducts; hog, meat byproducts; horse, meat byproducts; goat, meat byproducts; sheep, meat byproducts — 0.3 Milk — 0.1 Egg — 0.01 Poultry, meat — 0.01 Poultry, fat — 0.01

	Poultry, liver	0.05
Proposed import tolerances	Cotton, undelinted seed	0.06
	Vegetable, fruiting, group	0.2
	Tomato, paste	0.4
	Fruit, citrus, group	0.5
	Citrus, dried pulp	1.2
U.S. tolerances	Cotton, undelinted seed	0.60
	Cotton, gin byproducts	20.0
	Vegetable, leafy, except brassica, group	3.0
	Vegetable, brassica, leafy, group	1.20
	Vegetable, fruiting, group	0.20
	Tomato, paste	0.40
	Fruit, citrus, group	0.50
	Citrus, dried pulp	1.20
	Fruit, pome, group	1.0
	Grape	0.20
	Canola, seed	0.010
	Mustard, seed	0.010
	Cattle, meat; hog, meat; horse, meat; goat, meat; sheep, meat	0.10
	Cattle, fat; hog, fat; horse, fat; goat, fat; sheep, fat	0.10
	Cattle, meat byproducts; hog, meat byproducts; horse, meat byproducts; goat, meat byproducts; sheep, meat byproducts	0.30
	Milk	0.10
	Egg	0.010
	Poultry, meat	0.010
	Poultry, fat	0.010
	Poultry, liver	0.050
CODEX MRLs	None	
DRA DEEM™ Version 7.72 1994–1998 Continuing Survey of Food Intake for Individuals	It was estimated that the acute dietary exposure (95th percentile deterministic) to acetamiprid from food and water represented approximately 50.1% of the ARfD for children 1–6. The PDI for the remaining population subgroups, including infants, children, adults and seniors, each represented <50.1% of the ARfD. It was estimated that the chronic dietary exposure to acetamiprid from food and water represented approximately 78.4% of the ADI for the highest exposed subpopulation, which was children 1–6 when MRL values are used in the calculation. The PDI for the remaining population subgroups, including infants, children, adults and seniors, each represented <78.4% of the ADI. The carcinogenic potential of acetamiprid was assessed by the PMRA, which concluded that acetamiprid was not likely to be carcinogenic to humans. A cancer risk assessment is not required for this chemical. Consequently, the consumption estimates coupled with the MRLs indicate that there is adequate protection of the consumer, including infants, children, adults and seniors, from dietary residues of acetamiprid following use in accordance with GAP.	

Appendix V Environmental assessment

Table 1 Fate and behaviour of acetamiprid in the terrestrial environment

Fate process	End point	Interpretation
Hydrolysis	Stable to hydrolysis at pH 4, 5, 7 and 9 at 22°C Hydrolyzed at pH 9 at high temperature (35 and 45°C)	Hydrolysis will not be a route for transformation or dissipation of acetamiprid in the terrestrial environment.
Phototransformation on soil	Invalid study	Phototransformation is not likely to be an important route of transformation of acetamiprid.
Aerobic biotransformation	DT_{50}: ~1–8 d in soil	Acetamiprid is classed as non-persistent in soil under aerobic conditions.
Anaerobic biotransformation	No studies submitted	Based on the results of anaerobic aquatic biotransformation study, however, acetamiprid will be persistent under anaerobic conditions.
Adsorption/desorption	Adsorption K_{oc}: 157–298 mL/g carbon, for parent 153–1841 mL/g carbon, for IM-1-4 34–177 mL/g carbon, for IC-0	Acetamiprid has a moderate potential for mobility in soil. IM-1-4 has a low to moderate, and IC-0 has a very high to moderate, potential for mobility in soil.
Aged soil column leaching	No studies submitted	—
Field dissipation and leaching (Canada)	DT_{50}: 5.2–17.8 d No residues of parent compound and major transformation products below the 15 cm soil depth	Acetamiprid is non-persistent to slightly persistent in soil under field conditions. Acetamiprid and its major transformation products did not leach under conditions of the field study.

Table 2 Fate and behaviour of acetamiprid in the aquatic environment

Fate process	End point	Interpretation
Hydrolysis	Stable to hydrolysis at pH 4, 5, 7 and 9 at 22°C Hydrolyzed at pH 9 at high temperature (35 and 45°C)	Hydrolysis will not be a route for transformation or dissipation of acetamiprid in the aquatic environment.
Phototransformation	DT_{50} = 34 d in water	Phototransformation may be a minor route for transformation or dissipation of acetamiprid in the photic zone of clear natural water.
Aerobic biotransformation	DT_{50} = 30 d in water	Acetamiprid is classed as slightly persistent in water under aerobic conditions.
Anaerobic biotransformation	DT_{50} = 325 d in water	Acetamiprid is classed as persistent in water–sediment systems under anaerobic conditions.
Adsorption/desorption	Adsorption K_{oc} = 157–298 mL/g carbon	Acetamiprid has a potential for partitioning into the sediment.
Field dissipation	Not required	—

Table 3 Estimated environmental concentrations in drinking water

Groundwater	Reservoir		Dugout	
Acute and chronic	Acute[1]	Chronic[2]	Acute[1]	Chronic[2]
1.1 µg a.i./L	20.3 µg a.i./L	3.2 µg a.i./L	18.0 µg a.i./L	4.9 µg a.i./L

1 90th percentile of yearly peaks
2 90th percentile of yearly averages

Table 4 The maximum EECs of acetamiprid on vegetation and other food sources immediately following application at the rate of 428.4 g a.i./ha

Environmental compartment	Concentration fresh weight (mg a.i./kg)[a]	Fresh to dry weight ratios	Concentration dry weight (mg a.i./kg)
Short range grass	91.68	3.3[b]	302.54
Leaves and leafy crops	47.98	11[b]	527.78
Long grass	41.98	4.4[b]	184.72
Forage crops	51.4	5.4[b]	277.6
Small insects	22.27	3.8[c]	84.65
Pods with seeds	4.58	3.9[c]	17.87
Large insects	3.81	3.8[c]	14.48
Grain and seeds	3.81	3.8[c]	14.48
Fruit	5.74	7.6[c]	43.62

[a] Based on correlations reported in Hoerger and Kenaga (1972) and Kenaga (1973).

[b,c] Fresh to dry weight ratios from Harris[b] (1975) and Fletcher et al. (1994) and Spector[c] (1956).

Table 5 Summary of effects of acetamiprid on terrestrial organisms

Group [a]	Organism	Study	NOEL/NOEC	LD_{50}, LC_{50} or EC_{25}	Degree of toxicity
Birds	Mallard duck	Acute oral	<43 mg a.i./kg bw	84 mg a.i./kg bw	Moderately toxic
	Mallard duck	Dietary	Study determined to be scientifically invalid		
	Bobwhite quail	Acute oral	Not determined		
	Bobwhite quail	Reproduction	Study determined to be scientifically invalid		
	Bobwhite quail	Dietary	1000 mg a.i./kg diet	>5000 mg a.i./kg diet	Virtually nontoxic
	Mallard duck	Reproduction	NOEC = 250 mg a.i./kg diet	—	Treatment related effects such as decreased hatchling survivorship
Mammals	Rat	Acute oral	80 mg/kg bw	146 mg/kg bw	Highly toxic
	Rat	Dermal	—	>2000 mg/kg bw	Low toxicity
	Rat	Inhalation	—	>1.15 mg/L	Slightly toxic
	Beagle dog	Subchronic oral	16.7 mg/kg bw/d for ♂; 19.1 mg/kg bw/d for ♀	—	Toxic
	Rat	2-generation reproduction	17.9 mg/kg bw/d, for reproductive effects	—	Toxic
Soil organisms	Earthworm	Acute	Study determined to be scientifically invalid		
Beneficial arthropods	Honeybees	Acute oral	1.38 µg a.i./bee	14.5 µg a.i./bee	Moderately toxic
		Acute contact	6.25 µg a.i./bee	8.09 µg a.i./bee	Moderately toxic
Terrestrial plants	Seedling emergence	The most sensitive monocot species was onion, with an EC_{25} of 257.8 g a.i./ha, and the most sensitive dicot species was cucumber, with an EC_{25} of 179.3 g a.i./ha.			
	Vegetative vigour	The most sensitive monocot species was perennial ryegrass, with an EC_{25} of 515.6 g a.i./ha, and the most sensitive dicot species was lettuce, with an EC_{25} of 17.9 g a.i./ha.			

Table 6 Summary of toxicity of acetamiprid to aquatic organisms

Group	Organism	Study	NOEC	LC_{50}, EC_{50} or EC_{25}	Degree of toxicity
Fish	Rainbow trout	Acute	35 mg a.i./L	>100 mg a.i./L	Practically nontoxic
	Bluegill sunfish	Acute	<11.8 mg a.i./L	>119.3 mg a.i./L	Practically nontoxic
	Fathead minnow	early life-stages	19.2 mg a.i./L	95.8 mg a.i./L	Slightly toxic
	Sheepshead minnow	Acute	55 mg a.i./L	100 mg a.i./L	Slightly toxic
Invertebrates	Water flea	Acute	Study determined to be deficient/invalid		
	Water flea	Chronic	5 mg a.i./L	86 mg a.i./L	—
	Saltwater mysid	Acute	13 µg a.i./L	66 µg a.i./L	Very highly toxic
	Saltwater mysid	Chronic	2.5 µg a.i./L	3.4 µg a.i./L (MATC)	—
	Oyster shell deposition	Acute	<14 mg a.i./L	41 mg a.i./L	Slightly toxic
Algae	Blue-green alga	Acute	1.3 mg a.i./L	>1.3 mg a.i./L	—
	Green alga	Acute	1.2 mg a.i./L	>1.2 mg a.i./L	—
	Freshwater diatom	Acute	1.1 mg a.i./L	>1.1 mg a.i./L	—
	Marine diatom	Acute	1.0 mg a.i./L	>1.0 mg a.i./L	—
Plants	Duckweed	Acute	1.0 mg a.i./L	>1.0 mg a.i./L	—

Table 7 Summary of risk assessment for terrestrial organisms

Organism	Effect	NOEC or NOEL	EEC	MOS	Risk	Mitigative measures
Bobwhite quail	Reproductive	Study determined to be supplemental				
Mallard	Reproductive	250 mg a.i./kg diet	2.7 mg a.i./d	3.86	Low	Not required
Eastern cottontail	Acute (rat study)	80 mg/kg bw	13.31 mg a.i./d	—	Low	Not required
Masked shrew	Acute (rat study)	80 mg/kg bw	21.16–63.48 mg a.i./d	—	Low	Not required
Meadow vole	Acute (rat study)	80 mg/kg bw	44.92–72.61 mg a.i./d	—	Low	Not required
Earthworm	Acute	Invalid study				
Honeybees	Acute contact	6.25 µg a.i./bee	—	—	Moderate	Label statement
Terrestrial plants	Vegetative vigour	17.9 g a.i./ha	168 g a.i./ha	0.1	Moderate	Buffer zone

Table 8 Summary of risk assessment for aquatic organisms

Organism	Effect	NOEC or NOEL (mg a.i./L)	EEC (mg a.i./L)	MOS	Risk	Mitigatory measures
Water flea	Acute	Invalid study				
	Chronic	5	0.16	31.2	No risk	Not required
Saltwater mysid	Chronic	0.0025	0.16	0.015	High	Buffer zone
Bluegill sunfish	Acute	11.8	0.16	73.7	No risk	Not required
Green algae	Acute	1.2	0.16	7.5	No risk	Not required
Freshwater diatom	Acute	1.1	0.16	6.8	No risk	Not required
Duckweed	Acute	1	0.16	6.2	No risk	Not required

Appendix VI Value summary

Table 1 Approved use claims for Assail Brand 70 WP Insecticide

Crop	Pest	Approved rate		Seasonal maximum per crop site			Conclusion	Comments
		Product (g/ha)	a.i. (g/ha)	No. of applications	Product (g/ha)	a.i. (g/ha)		
Leafy vegetables, crop grop 4: amaranth leafy, arugula, cardoon, celery, celery (Chinese), celtuce, chervil, chrysanthemum (edible-leaved), chrysanthemum (garland), corn salad, cress (garden), cress (upland), dandelion leaves, dock, endive, fennel (Florence), lettuce (head and leaf), orach, parsley leaves, purslane (garden), purslane (winter), radicchio, rhubarb, spinach, spinach (New Zealand), Spinach (vine), Swiss chard	Aphids	56–86	39–60	5	430	300	Use supported with limitation	Additional data are required to establish LER

Crop	Pest	Approved rate		Seasonal maximum per crop site			Conclusion	Comments
		Product (g/ha)	a.i. (g/ha)	No. of applications	Product (g/ha)	a.i. (g/ha)		
Cole crops, crop group 5: broccoli, broccoli (Chinese), broccoli raab, Brussels sprouts, cabbage, cabbage (Chinese, bok choy), cabbage (Chinese, napa), cabbage (Chinese mustard, gai choy), cauliflower, cavalo broccolo, collards, citrus (dried pulp), kale, kohlrabi, mizuna, mustard greens, mustard spinach, rape greens	Aphids	56–86	39–60	5	600	420	Uses supported with limitation	Additional data are required to establish LER
	Whitefly	120	84					
Tomato, field	Aphids	56–86	39–60	4 see comments	480	336	Uses supported with limitation	Additional data are required to establish LER
	Whitefly	120	84					
	Colorado potato beetle	80	56				Use fully supported	Seasonal number of applications are limited to 2 for control of CPB
Pome fruits, crop group 11: apple, crabapple, pear (oriental), quince	Aphids	80–120	56–84	4	960	672	Uses supported with limitation	Additional data are required to establish LER
	Tentiform leafminer	80	56					
	Pear psylla	67–240	47–168					Additional data are required to confirm the need and criteria for use of the higher rate
	Codling moth	120–240	84–168				Uses fully supported	

Crop	Pest	Approved rate		Seasonal maximum per crop site			Conclusion	Comments
		Product (g/ha)	a.i. (g/ha)	No. of applications	Product (g/ha)	a.i. (g/ha)		
	Leafhoppers	80	56					
Grapes	Leafhoppers	80	56	2	160	112	Use fully supported	

Table 2 Approved use claims for Chipco Brand Tristar 70 WSP Insecticide

Crop	Pest	Approved rate (per 1000 L spray volume)		Seasonal maximum per crop site			Conclusion	Comments
		Product (packs)[a]	a.i. (g)	No. of applications	Product (packs/ha)	a.i. (g/ha)		
Lathhouse, shadehouse, greenhouse and outdoor non-food flowering and ornamental plants	Aphids	2.5	28	2 (greenhouse, shadehouse, lathhouse) or 5 (outdoor)	20 (greenhouse, shadehouse, lathhouse) or 50 (outdoor)	224 (greenhouse, shadehouse, lathhouse) or 560 (outdoor)	Uses fully supported	
	Whitefly	5–10	56–112					
	Leafhoppers	5	56					
	European pine sawfly	2.5	28				Uses supported with limitation	Additional data are required to establish LER
	Tentiform leafminer	5	56					

[a] One pack contains 16 g of the product

Table 3 Approved use claims for Pristine Brand RTU Insecticide[a]

Crop	Pest	Seasonal maximum no. of applications per crop site	Conclusion
Leafy vegetables, crop group 4: amaranth leafy, arugula, cardoon, celery, celery (Chinese), celtuce, chervil, chrysanthemum (edible-leaved), chrysanthemum (garland), corn salad, cress (garden), cress (upland), dandelion leaves, dock, endive, fennel (Florence), lettuce, orach, parsley leaves, purslane (garden), purslane (winter), radicchio, rhubarb, spinach, spinach (New Zealand), spinach (vine), Swiss chard	Aphids	5	Uses fully supported
Cole crops, crop group 5: broccoli, broccoli (Chinese), Brussels sprouts, cabbage, cabbage (Chinese, bok choy), cabbage (Chinese, napa), cabbage (Chinese mustard, gai choy), cauliflower, collards, citrus (dried pulp), kale, kohlrabi, mizuna, mustard greens, mustard spinach, rape greens	Aphids Whitefly	5	
Tomato, field	Aphids Whitefly Colorado potato beetle	5	
Pome fruit, crop group 11: apple, crabapple, pear, pear (oriental), quince	Aphids Leafhoppers Tentiform leafminer	5	
Outdoor flowering and ornamental plants	Aphids Leafhoppers European pine sawfly Tentiform leafminer Whitefly	5	

[a] This is a domestic RTU product, which is applied undiluted with 0.006% acetamiprid.